QUINAZOLINONE MODULATORS OF NUCLEAR RECEPTORS

FIELD OF THE INVENTION

Quinazolinones, compositions containing quinazolinones and methods for modulating the activity of nuclear receptors using quinazolinones are provided. In particular, quinazolinones are provided for modulating the activity of FXR and orphan nuclear receptors.

BACKGROUND OF THE INVENTION

Nuclear Receptors

Nuclear receptors are a superfamily of regulatory proteins that are structurally and functionally related and are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones (see, *e.g.*, Evans (1988) *Science 240*:889-895). These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in response to ligands for the receptors.

Nuclear receptors can be classified based on their DNA binding properties (see, *e.g.*, Evans, *supra* and Glass (1994) *Endocr. Rev. 15*:391-407). For example, one class of nuclear receptors includes the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors which bind as homodimers to hormone response elements (HREs) organized as inverted repeats (see, *e.g.*, Glass, *supra*). A second class of receptors, including those activated by retinoic acid, thyroid hormone, vitamin D_3, fatty acids/peroxisome proliferators (*i.e.*, peroxisome proliferator activated receptor (PPAR)) and ecdysone, bind to HREs as heterodimers with a common partner, the retinoid X receptors (*i.e.*, RXRs, also known as the 9-*cis* retinoic acid receptors; see, *e.g.*, Levin *et al.* (1992) *Nature 355*:359-361 and Heyman *et al.* (1992) *Cell 68*:397-406).

RXRs are unique among the nuclear receptors in that they bind DNA as a homodimer and are required as a heterodimeric partner for a number of additional nuclear receptors to bind DNA (see, *e.g.*, Mangelsdorf *et al.* (1995) *Cell 83*:841-850). The latter receptors, termed the class II nuclear receptor subfamily, include many

which are established or implicated as important regulators of gene expression. There are three RXR genes (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev.* 6:329-344), coding for RXRα, -β, and -γ, all of which are able to heterodimerize with any of the class II receptors, although there appear to be preferences for distinct RXR subtypes by partner receptors *in vivo* (see, *e.g.*, Chiba *et al.* (1997) *Mol. Cell. Biol.* 17:3013-3020). In the adult liver, RXRα is the most abundant of the three RXRs (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev.* 6:329-344), suggesting that it might have a prominent role in hepatic functions that involve regulation by class II nuclear receptors. See also, Wan *et al.* (2000) *Mol. Cell. Biol. 20*:4436-4444.

Orphan Nuclear Receptors

Included in the nuclear receptor superfamily of regulatory proteins are nuclear receptors for whom the ligand is known and those which lack known ligands. Nuclear receptors falling in the latter category are referred to as orphan nuclear receptors. The search for activators for orphan receptors has led to the discovery of previously unknown signaling pathways (see, *e.g.*, Levin *et al.*, (1992), *supra* and Heyman *et al.*, (1992), *supra*). For example, it has been reported that bile acids, which are involved in physiological processes such as cholesterol catabolism, are ligands for FXR (*infra*).

Since it is known that products of intermediary metabolism act as transcriptional regulators in bacteria and yeast, such molecules may serve similar functions in higher organisms (see, e.g., Tomkins (1975) Science 189:760-763 and O'Malley (1989) Endocrinology 125:1119-1120). For example, one biosynthetic pathway in higher eukaryotes is the mevalonate pathway, which leads to the synthesis of cholesterol, bile acids, porphyrin, dolichol, ubiquinone, carotenoids, retinoids, vitamin D, steroid hormones and farnesylated proteins.

FXR

FXR (originally isolated as RIP14 (retinoid X receptor-interacting protein-14), see, *e.g.*, Seol *et al.* (1995) *Mol. Endocrinol. 9*:72-85) is a member of the nuclear hormone receptor superfamily and is primarily expressed in the liver, kidney

and intestine (see, *e.g.*, Seol *et al.*, *supra* and Forman *et al.* (1995) *Cell 81*:687-693). It functions as a heterodimer with the retinoid X receptor (RXR) and binds to response elements in the promoters of target genes to regulate gene transcription. The FXR-RXR heterodimer binds with highest affinity to an inverted repeat-1 (IR-1) response element, in which consensus receptor-binding hexamers are separated by one nucleotide. FXR is part of an interrelated process, in that FXR is activated by bile acids (the end product of cholesterol metabolism) (see, *e.g.*, Makishima *et al.* (1999) *Science 284*:1362-1365, Parks *et al.* (1999) *Science 284*:1365-1368, Wang *et al.* (1999) *Mol. Cell. 3*:543-553), which serve to inhibit cholesterol catabolism. See also, Urizar *et al.* (2000) *J. Biol. Chem. 275*:39313-39317.

Nuclear Receptors and Disease

Nuclear receptor activity, including FXR and / or orphan nuclear receptor activity has been implicated in a variety of diseases and disorders, including, but not limited to, hypercholesterolemia, and complications thereof, including including without limitation coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis and xanthoma, (see, *e.g.*, International Patent Application Publication No. WO 00/57915), osteoporosis and vitamin deficiency (see, *e.g.*, U.S. Patent No. 6,316,5103), hyperlipoproteinemia (see, *e.g.*, International Patent Application Publication No. WO 01/60818), hypertriglyceridemia, lipodystrophy, peripheral occlusive disease, ischemic stroke, hyperglycemia and diabetes mellitus (see, *e.g.*, International Patent Application Publication No. WO 01/82917), disorders related to insulin resistance including the cluster of disease states, conditions or disorders that make up "Syndrome X" such as glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, hypertension, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plasminogen activator inhibitor-1, atherosclerosis and gallstones (see, *e.g.*, International Patent Application Publication No. WO 00/37077), disorders of the skin and mucous membranes (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. WO 98/32444), obesity, acne (see, *e.g.*, International Patent Application

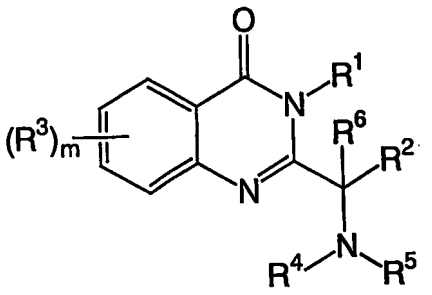
Publication No. WO 00/49992), and cancer, Parkinson's disease and Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334). The activity of nuclear receptors, including FXR and/or orphan nuclear receptors, has been implicated in physiological processes including, but not limited to, bile acid biosynthesis, cholesterol metabolism or catabolism, and modulation of cholesterol 7α-hydroxylase gene (CYP7A1) transcription (see, *e.g.*, Chiang *et al.* (2000) *J. Biol. Chem.* 275:10918-10924), HDL metabolism (see, *e.g.*, Urizar *et al.* (2000) *J. Biol. Chem.* 275:39313-39317), hyperlipidemia, cholestasis, and increased cholesterol efflux and increased expression of ATP binding cassette transporter protein (ABC1) (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Thus, there is a need for compounds, compositions and methods of modulating the activity of nuclear receptors, including FXR and/or orphan nuclear receptors. Such compounds are useful in the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders in which nuclear receptor activity is implicated.

SUMMARY OF THE INVENTION

Compounds for use in compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating farnesoid X receptor (FXR) and/or orphan nuclear receptors, are provided. In certain embodiments, the compounds are quinazolinones. In one embodiment, the compounds provided herein are agonists of FXR. In another embodiment, the compounds provided herein are antagonists of FXR. Agonists that exhibit low efficacy are, in certain embodiments, antagonists. Antagonists include both competitive and non-competitive antagonists. In another embodiment the compound is an inverse agonist, partial agonist or partial antagonist

In one embodiment, the compounds for use in the compositions and methods provided herein have formula (I):



(I)

wherein:

m is an integer from 0 to 4;

R^1 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-OR^7$ or $-N(R^8)R^9$, with the proviso that R^1 is not 3- or 4-(1,1,1,3,3,3-hexafluoro-2-hydroxy-2-propyl)phenyl;

R^2, R^4, R^5 and R^6 are selected from (a) and (b) as follows:

(a) R^2 and R^6 are selected from (i) and (ii) as follows: (i) R^2 and R^6 are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, or optionally substituted heterocyclylalkyl; or (ii) R^2 and R^6 together form optionally substituted alkylene or optionally substituted alkenylene; and

R^4 and R^5 are selected from (i) and (ii) as follows: (i) R^4 and R^5 are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-N(R^8)R^9$, $-OR^7$, $-S(O)_jR^{11}$ where j is 1 or 2, $-B(R^{22})_2$, $-P(R^{22})_2$, $-P(O)(R^{22})_2$ and $-C(E)R^{23}$, where E is selected from O, S and NR^7; or (ii) R^4 and R^5 together form optionally substituted alkylene,

optionally substituted alkenylene, optionally substituted alkyleneoxyalkylene or optionally substituted alkyleneazaalkylene; or

(b) R^2 and R^5, or R^2 and R^4, or R^6 and R^5, or R^6 and R^4, together form a 4, 5, 6 or 7 membered optionally substituted heterocyclyl group, or a 5 or 6 membered optionally substituted heteroaryl group; and the remainder of R^2, R^4, R^5 and R^6 are each independently selected as in (i) above;

each R^3 is independently selected from the group consisting of halo, pseudohalo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-N(R^{12})R^{13}$, $-OR^{14}$, $-C(E)R^{15}$ where E is O, S or NR^7, and $-S(O)_yR^{16}$ where y is 0, 1 or 2;

or any two R^3 groups, which substitute adjacent carbons on the ring, together form optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkylenedioxy, optionally substituted thioalkylenoxy, or optionally substituted alkylenedithioxy;

each R^7 is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, and optionally substituted heterocyclylalkyl;

R^8 and R^9 are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-S(O)_jR^{10}$ where j is 1 or 2, and $-C(M)R^{11}$, where M is selected from O and S;

or R^8 and R^9 together form alkylene, alkenylene, alkyleneoxyalkylene or

alkyleneazaalkylene;

each R^{10} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, and optionally substituted heterocyclylalkyl;

each R^{11} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-OR^{10}$ and $-N(R^7)_2$;

R^{12} and R^{13} are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-C(M)R^{17}$ where M is O or S, and $-S(O)_jR^{18}$ where j is 1 or 2;

or R^{12} and R^{13} together form optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkyleneoxyalkylene or optionally substituted alkyleneazaalkylene;

R^{14} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl or $-C(M)R^{17}$ where M is O or S;

R^{15} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted

cycloalkylalkyl, optionally substituted heterocyclylalkyl, -OH, -OR^{14} or -$N(R^{12})R^{13}$;

R^{16} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, -OH, -OR^{19} or -$N(R^{20})R^{21}$;

R^{17} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, -OR^{19} or -$N(R^{20})R^{21}$;

R^{18} is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, -OR^{19} or -$N(R^{20})R^{21}$;

R^{19} is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R^{20} and R^{21} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl,

or R^{20} and R^{21} together form alkylene, alkenylene, alkyleneoxyalkylene or alkyleneazaalkylene;

each R^{22} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, -OR^{7} and -$N(R^{7})_2$;

R^{23} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted

heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, --OR^{10}, -$N(R^7)_2$, or -$N(R^7)N(R^7)_2$;

wherein each of the above R^1-R^{23} groups, when substituted, are substituted with one or more substituents each independently selected from Q^1, where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, carboxy, carboxyalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, cycloalkylcarbonyl, heterocyclylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, -$N^+(R^{24})_3$, -$P(R^{25})_2$, -$P(O)(R^{25})_2$, -$OP(O)(R^{25})_2$, -$N(R^{24})C(O)R^{26}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, carboxyalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy,

arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_y-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_y-O-$) or alkylenedithioxy (*i.e.*, $-S-(CH_2)_y-S-$) where y is 1 or 2; or two Q^1 groups, which substitute the same atom, together form alkylene;

each R^{24} is independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl;

each R^{25} is independently selected from the group consisting of hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl and $-N(R^{27})R^{28}$,

R^{26} is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-N(R^{27})R^{28}$;

R^{27} and R^{28} are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl,

or R^{27} and R^{28} together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;

and each Q^1 is optionally substituted by one or more substituents selected from Q^2; where each Q^2 is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, carboxy, carboxyalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, cycloalkoxy, perfluoroalkoxy,

alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^{+}(R^{24})_3$, $-P(R^{25})_2$, $-P(O)(R^{25})_2$, $-OP(O)(R^{25})_2$, $-N(R^{24})C(O)R^{26}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, carboxyalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^2 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_y-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_y-O-$) or alkylenedithioxy (*i.e.*, $-S-(CH_2)_y-S-$) where y is 1 or 2; or two Q^2 groups, which substitute the same atom, together form alkylene,

where R^{24}, R^{25}, R^{26}, R^{27} and R^{28} are as defined above;

as a stereoisomer, racemate or mixture thereof; or as a pharmaceutically acceptable derivative thereof.

In one embodiment, R^1 is optionally substituted phenyl, and is selected with the proviso that it is not substituted at the 3 or 4 position with $-C(OH)(CF_3)_2$.

The groups R^1, R^2, R^3, R^4, and R^5 are selected such that the resulting compound has nuclear receptor modulation activity, such as in at least one assay

described herein, such as FXR antagonist or agonist activity, and, in certain embodiments, at an IC_{50} or EC_{50} of less than about 100 μM. The FXR IC_{50} or EC_{50} values for the compounds provided herein are, in certain embodiments, less than about 50 μM, 25 μM, 10 μM, 1 μM, 100 nM, 10 nM or 1 nM.

Also of interest are any pharmaceutically-acceptable derivatives, including salts, esters, enol ethers, enol esters, solvates, hydrates and prodrugs of the compounds described herein. Pharmaceutically-acceptable salts, include, but are not limited to, amine salts, such as but not limited to *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, *N*-methylglucamine, procaine, *N*-benzylphenethylamine, 1-*para*-chlorobenzyl-2-pyrrolidin-1'-ylmethyl-benzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc, aluminum, and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

Pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof, that deliver amounts effective for the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders that are modulated or otherwise affected by nuclear receptor activity, including FXR and/or orphan nuclear receptor activity, or in which nuclear receptor activity, including FXR and/or orphan nuclear receptor activity, is implicated, are also provided. The effective amounts and concentrations are effective for ameliorating any of the symptoms of any of the diseases or disorders.

Methods for treatment, prevention, or amelioration of one or more symptoms of diseases or disorders mediated by or in which nuclear receptor activity, including FXR and/or orphan nuclear receptor activity, is implicated, are provided.

Such methods include methods of treatment, prevention and amelioration of one or more symptoms of hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, obesity, disease states associated with elevated cholesterol levels, including without limitation, coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, disorders related to insulin resistance, including without limitation, xanthoma, glucose intolerance, an increase in plasma triglyceride and a decrease in high density lipoprotein cholesterol concentrations, hypertension, hyperuricemia, smaller density lipoprotein particles, and higher circulating levels of plasminogen activator inhibitor-1, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, or cardiovascular disorders, using one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof.

Methods of modulating the activity of nuclear receptors, including FXR and/or orphan nuclear receptors, using the compounds and compositions provided herein are also provided. The compounds and compositions provided herein are active in assays that measure the activity of nuclear receptors, including FXR and/or orphan nuclear receptors, including the assays provided herein. These methods include inhibiting and up-regulating the activity of nuclear receptors, including FXR and/or orphan nuclear receptors.

Methods of reducing cholesterol levels in a subject in need thereof by administration of one or more compounds or compositions provided herein are also provided.

Methods of modulating cholesterol metabolism using the compounds and compositions provided herein are provided.

Methods of treating, preventing, or ameliorating one or more symptoms of diseases or disorders which are affected by cholesterol, triglyceride, or bile acid levels by administration of one or more of the compounds and compositions provided

herein are also provided.

In practicing the methods, effective amounts of the compounds or compositions containing therapeutically effective concentrations of the compounds, which are formulated for systemic delivery, including parenteral, oral, or intravenous delivery, or for local or topical application, for the treatment of nuclear receptor, including FXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR and/or orphan nuclear receptor activity, is implicated, including, but not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, or cardiovascular disorders, are administered to an individual exhibiting the symptoms of these diseases or disorders. The amounts are effective to ameliorate or eliminate one or more symptoms of the diseases or disorders.

Articles of manufacture containing packaging material, a compound or composition, or pharmaceutically acceptable derivative thereof, provided herein, which is effective for modulating the activity of nuclear receptors, including FXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR and/or orphan nuclear receptor activity, is implicated, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including FXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR and/or orphan nuclear

receptor activity, is implicated, are provided.

DETAILED DESCRIPTION OF EMBODIMENTS

A. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All cited patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, a nuclear receptor is a member of a superfamily of regulatory proteins that are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones. These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in response to a ligand therefor. Nuclear receptors may be classified based on their DNA binding properties. For example, the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors bind as homodimers to hormone response elements (HREs) organized as inverted repeats. Another example are receptors, including those activated by retinoic acid, thyroid hormone, vitamin D_3, fatty acids/peroxisome proliferators and ecdysone, that bind to HREs as heterodimers with a common partner, the retinoid X receptor (RXR). Among the latter receptors are FXR.

As used herein, an orphan nuclear receptor is a gene product that embodies the structural features of a nuclear receptor that was identified without any prior knokledge of their association with a putative ligand and/or for which the natural ligand is unknown. Under this definition, orphan nuclear receptors include, without limitation, farnesoid X receptor (FXR), liver X receptor (LXR α & β), retinoid X receptor (RXRα, β & γ), and peroxisome proliferator activator receptor (PPAR α, β, & γ)(see, Giguere (1999) Endocrine Reviews 20 (5): 689-725).

As used herein, farnesoid X receptor or FXR refers to all mammalian forms of such receptor including, for example, alternative splice isoforms and naturally

occurring isoforms (see, e.g. Huber *et al* (2002) *Gene* 290:35-43). Representative FXR species include, without limitation rat FXR (GenBank Accession No. NM_021745), mouse FXR (Genbank Accession No. NM_009108), and human FXR (GenBank Accession No. NM_005123).

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, *N*-methylglucamine, procaine, *N*-benzylphenethylamine, 1-*para*-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula C=C(OR) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl ar heterocyclyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula C=C(OC(O)R) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl,

heteroaralkyl, cycloalkyl ar heterocyclyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

As used herein, treatment means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating a nuclear receptor, including FXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR and/or orphan nuclear receptor activity, is implicated.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as modulation of FXR activity, in an assay that measures such response.

As used herein, EC_{50} refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

As used herein, a prodrug is a compound that, upon *in vivo* administration, is metabolized by one or more steps or processes or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. Prodrugs of a compound of the invention may be prepared by modifying functional groups present in the compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound of the invention. Prodrugs include compounds of the invention wherein a hydroxy, amino or

mercapto group is bonded to any group that, when the prodrug of the compound of the invention is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention and the like.

The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, *e.g.*, Nogrady (1985) *Medicinal Chemistry. A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (*R*) or (*S*) configuration, or may be a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. In the case of amino acid residues, such residues may be of either the L- or D-form. The configuration for naturally occurring amino acid residues is generally L. When not specified the residue is the L form. As used herein, the term "amino acid" refers to α-amino acids which are racemic, or of either the D- or L-configuration. The designation "d" preceding an amino acid designation (*e.g.*, dAla, dSer, dVal, etc.) refers to the D-isomer of the amino acid. The designation "dl" preceding an amino acid designation (*e.g.*, dlPip) refers to a mixture of the L- and D-isomers of the amino acid. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization *in vivo*. As such, one of skill in the art will recognize that administration of a compound in its (*R*) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (*S*) form. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

As used herein, substantially pure means sufficiently homogeneous to

appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC.

As used herein, the nomenclature alkyl, alkoxy, carbonyl, etc. is used as is generally understood by those of skill in this art.

As used herein, alkyl, alkenyl and alkynyl carbon chains, if not specified, contain from 1 to 20 carbons, or 1 to 16 carbons, and are straight or branched. Alkenyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 double bonds, and the alkenyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 double bonds. Alkynyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 triple bonds, and the alkynyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 triple bonds. Exemplary alkyl, alkenyl and alkynyl groups herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, sec-butyl, *tert*-butyl, isopentyl, neopentyl, *tert*-penytyl and isohexyl. As used herein, lower alkyl, lower alkenyl, and lower alkynyl refer to carbon chains having from about 1 or about 2 carbons up to about 6 carbons. As used herein, "alk(en)(yn)yl" refers to an alkyl group containing at least one double bond and at least one triple bond.

As used herein, "cycloalkyl" refers to a saturated mono- or multicyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments of 3 to 6 carbon atoms; cycloalkenyl and cycloalkynyl refer to mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond.

Cycloalkenyl and cycloalkynyl groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenyl groups, in further embodiments, containing 4 to 7 carbon atoms and cycloalkynyl groups, in further embodiments, containing 8 to 10 carbon atoms. The ring systems of the cycloalkyl, cycloalkenyl and cycloalkynyl groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)yl" refers to a cycloalkyl group containing at least one double bond and at least one triple bond.

As used herein, "substituted alkyl," "substituted alkenyl," "substituted alkynyl," "substituted cycloalkyl," "substituted cycloalkenyl," and "substituted cycloalkynyl" refer to alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl and cycloalkynyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three or four substituents, where the substituents are as defined herein, generally selected from Q^1 as defined above in the Summary of the Invention.

As used herein, "aryl" refers to aromatic monocyclic or multicyclic groups containing from 6 to 19 carbon atoms. Aryl groups include, but are not limited to groups such as fluorenyl, substituted fluorenyl, phenyl, substituted phenyl, naphthyl and substituted naphthyl.

As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 15 members where one or more, in one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrrolidinyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, *N*-methylpyrrolyl, quinolinyl and isoquinolinyl.

As used herein, a "heteroarylium" group is a heteroaryl group that is positively charged on one or more of the heteroatoms.

As used herein, "heterocyclyl" refers to a monocyclic or multicyclic non-aromatic ring system, in one embodiment of 3 to 10 members, in another embodiment of 4 to 7 members, in a further embodiment of 5 to 6 members, where one or more, in certain embodiments, 1 to 3, of the atoms in the ring system is a heteroatom, that is,

an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. In embodiments where the heteroatom(s) is(are) nitrogen, the nitrogen is optionally substituted with alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, acyl, guanidino, or the nitrogen may be quaternized to form an ammonium group where the substituents are selected as above.

As used herein, "substituted aryl," "substituted heteroaryl" and "substituted heterocyclyl" refer to aryl, heteroaryl and heterocyclyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three or four substituents, where the substituents are as defined herein, generally selected from Q^1 as defined above in the Summary of the Invention.

As used herein, "aralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl group.

As used herein, "heteroaralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by a heteroaryl group.

As used herein, "halo", "halogen" or "halide" refers to F, Cl, Br or I.

As used herein, pseudohalides or pseudohalo groups are groups that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides. Pseudohalides include, but are not limited to, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, and azide.

As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl, trifluoromethyl and 1-chloro-2-fluoroethyl.

As used herein, "haloalkoxy" refers to -OR in which R is a haloalkyl group.

As used herein, "sulfinyl" or "thionyl" refers to -S(O)-. As used herein, "sulfonyl" or "sulfuryl" refers to $-S(O)_2-$. As used herein, "sulfo" refers to $-S(O)_2O-$.

As used herein, "oxycarbonyl" or "carbonyloxy" refers to a divalent radical, -C(O)O-.

As used herein, "aminocarbonyl" refers to $-C(O)NH_2$.

As used herein, "alkylaminocarbonyl" refers to -C(O)N(H)R in which R is alkyl, including lower alkyl. As used herein, "dialkylaminocarbonyl" refers to -C(O)N(R')R in which R' and R are independently alkyl, including lower alkyl; "carboxamide" refers to groups of formula -N(R')C(O)R in which R' and R are independently alkyl, including lower alkyl.

As used herein, "diarylaminocarbonyl" refers to -C(O)N(R)R' in which R and R' are independently selected from aryl, including lower aryl, such as phenyl.

As used herein, "arylalkylaminocarbonyl" refers to -C(O)N(R)R' in which one of R and R' is aryl, including lower aryl, such as phenyl, and the other of R and R' is alkyl, including lower alkyl.

As used herein, "arylaminocarbonyl" refers to -C(O)N(H)R in which R is aryl, including lower aryl, such as phenyl.

As used herein, "carboxy" refers to -C(O)OH.

As used herein, "alkoxycarbonyl" refers to -C(O)OR in which R is alkyl, including lower alkyl.

As used herein, "aryloxycarbonyl" refers to -C(O)OR in which R is aryl, including lower aryl, such as phenyl.

As used herein, "alkoxy" and "alkylthio" refer to -OR and -SR, in which R is alkyl, including lower alkyl.

As used herein, "aryloxy" and "arylthio" refer to -OR and -OR, in which R is aryl, including lower aryl, such as phenyl.

As used herein, "aralkoxy" refers to -OR in which R is aralkyl, such as benzyl.

As used herein, "alkylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 1 to about 20 carbon atoms, in another embodiment having from 1 to 12 carbons. In a further embodiment alkylene includes lower alkylene. There may be optionally inserted along the alkylene group one or more oxygen, sulfur, including S(=O) and $S(=O)_2$ groups, or optionally substituted nitrogen atoms, including -NR- and $-N^+RR-$ groups, where the nitrogen substituent(s) is(are) alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or COR', where R' is alkyl, aryl, aralkyl, heteroaryl,

heteroaralkyl, -OY or -NYY, where Y is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl. Alkylene groups include, but are not limited to, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-(CH_2)_3-$), methylenedioxy ($-O-CH_2-O-$) and ethylenedioxy ($-O-(CH_2)_2-O-$). The term "lower alkylene" refers to alkylene groups having 1 to 6 carbons. In certain embodiments, alkylene groups are lower alkylene, including alkylene of 1 to 3 carbon atoms.

As used herein, "azaalkylene" refers to $-(CRR)_n-NR-(CRR)_m-$, where n and m are each independently an integer from 0 to 4. As used herein, "oxaalkylene" refers to $-(CRR)_n-O-(CRR)_m-$, where n and m are each independently an integer from 0 to 4. As used herein, "thiaalkylene" refers to $-(CRR)_n-S-(CRR)_m-$, $-(CRR)_n-S(=O)-(CRR)_m-$, and $-(CRR)_n-S(=O)_2-(CRR)_m-$, where n and m are each independently an integer from 0 to 4.

As used herein, "alkenylene" refers to a straight, branched or cyclic, in one embodiment straight or branched, divalent aliphatic hydrocarbon group, in certain embodiments having from 2 to about 20 carbon atoms and at least one double bond, in other embodiments 1 to 12 carbons. In further embodiments, alkenylene groups include lower alkenylene. There may be optionally inserted along the alkenylene group one or more oxygen, sulfur or optionally substituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkenylene groups include, but are not limited to, —CH=CH— CH=CH— and $-CH=CH-CH_2-$. The term "lower alkenylene" refers to alkenylene groups having 2 to 6 carbons. In certain embodiments, alkenylene groups are lower alkenylene, including alkenylene of 3 to 4 carbon atoms.

As used herein, "alkynylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 2 to about 20 carbon atoms and at least one triple bond, in another embodiment 1 to 12 carbons. In a further embodiment, alkynylene includes lower alkynylene. There may be optionally inserted along the alkynylene group one or more oxygen, sulfur or optionally substituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkynylene groups include, but are not limited to, —C≡C—C≡C—, $-C\equiv C-$ and $-C\equiv C-CH_2-$. The term "lower alkynylene" refers to alkynylene groups having 2 to 6 carbons. In certain embodiments, alkynylene groups are lower alkynylene,

including alkynylene of 3 to 4 carbon atoms.

As used herein, "alk(en)(yn)ylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 2 to about 20 carbon atoms and at least one triple bond, and at least one double bond; in another embodiment 1 to 12 carbons. In further embodiments, alk(en)(yn)ylene includes lower alk(en)(yn)ylene. There may be optionally inserted along the alkynylene group one or more oxygen, sulfur or optionally substituted nitrogen atoms, where the nitrogen substituent is alkyl. Alk(en)(yn)ylene groups include, but are not limited to, $-C{=}C-(CH_2)_n-C{\equiv}C-$, where n is 1 or 2. The term "lower alk(en)(yn)ylene" refers to alk(en)(yn)ylene groups having up to 6 carbons. In certain embodiments, alk(en)(yn)ylene groups have about 4 carbon atoms.

As used herein, "cycloalkylene" refers to a divalent saturated mono- or multicyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments 3 to 6 carbon atoms; cycloalkenylene and cycloalkynylene refer to divalent mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond. Cycloalkenylene and cycloalkynylene groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenylene groups in certain embodiments containing 4 to 7 carbon atoms and cycloalkynylene groups in certain embodiments containing 8 to 10 carbon atoms. The ring systems of the cycloalkylene, cycloalkenylene and cycloalkynylene groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)ylene" refers to a cycloalkylene group containing at least one double bond and at least one triple bond.

As used herein, "substituted alkylene," "substituted alkenylene," "substituted alkynylene," "substituted cycloalkylene," "substituted cycloalkenylene," and "substituted cycloalkynylene" refer to alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene and cycloalkynylene groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three or four substituents, where the substituents are as defined herein, generally selected from Q^1 as defined above in the Summary of the Invention.

As used herein, "arylene" refers to a monocyclic or polycyclic, in certain

embodiments monocyclic, divalent aromatic group, in one embodiment having from 5 to about 20 carbon atoms and at least one aromatic ring, in another embodiment 5 to 12 carbons. In further embodiments, arylene includes lower arylene. Arylene groups include, but are not limited to, 1,2-, 1,3- and 1,4-phenylene. The term "lower arylene" refers to arylene groups having 5 or 6 carbons.

As used herein, "heteroarylene" refers to a divalent monocyclic or multicyclic aromatic ring system, in one embodiment of about 5 to about 15 members where one or more, in certain embodiments 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "heterocyclylene" refers to a divalent monocyclic or multicyclic non-aromatic ring system, in certain embodiments of 3 to 10 members, in one embodiment 4 to 7 members, in another embodiment 5 to 6 members, where one or more, including 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "substituted arylene," "substituted heteroarylene" and "substituted heterocyclylene" refer to arylene, heteroarylene and heterocyclylene groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three of four substituents, where the substituents are as defined herein, generally selected from Q^1 as defined above in the Summary of the Invention.

As used herein, "alkylidene" refers to a divalent group, such as =CR'R", which is attached to one atom of another group, forming a double bond. Alkylidene groups include, but are not limited to, methylidene ($=CH_2$) and ethylidene ($=CHCH_3$). As used herein, "arylalkylidene" refers to an alkylidene group in which either R' or R" is an aryl group. "Cycloalkylidene" groups are those where R' and R" are linked to form a carbocyclic ring. "Heterocyclylidene" groups are those where at least one of R' and R" contain a heteroatom in the chain, and R' and R" are linked to form a heterocyclic ring.

As used herein, "amido" refers to the divalent group -C(O)NH-. "Thioamido" refers to the divalent group -C(S)NH-. "Oxyamido" refers to the divalent group -OC(O)NH-. "Thiaamido" refers to the divalent group -SC(O)NH-. "Dithiaamido" refers to the divalent group -SC(S)NH-. "Ureido" refers to the divalent group -

HNC(O)NH-. "Thioureido" refers to the divalent group -HNC(S)NH-.

As used herein, "semicarbazide" refers to -NHC(O)NHNH-. "Carbazate" refers to the divalent group -OC(O)NHNH-. "Isothiocarbazate" refers to the divalent group -SC(O)NHNH-. "Thiocarbazate" refers to the divalent group -OC(S)NHNH-. "Sulfonylhydrazide" refers to the group -SO_2NHNH-. "Hydrazide" refers to the divalent group -C(O)NHNH-. "Azo" refers to the divalent group -N=N-. "Hydrazinyl" refers to the divalent group -NH-NH-.

Where the number of any given substituent is not specified (*e.g.*, "haloalkyl"), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens. As another example, "C_{1-3}alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three carbons.

As used herein, the following terms have their accepted meaning in the chemical literature:

AcOH	acetic acid
Cbz	benzyl carbamate
CDI	carbonyl diimidazole
$CHCl_3$	chloroform
conc	concentrated
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
EtOH	ethanol (100%)
Et_2O	diethyl ether
Hex	hexanes
H_2SO_4	sulfuric acid
MeCN	acetonitrile
MeOH	methanol

Pd (0)	palladium (0)
Pd/C	palladium on activated carbon
PPh_3	triphenyl phosphine
TEA	triethylamine
THF	tetrahydrofuran
TFA	trifluoroacetic acid

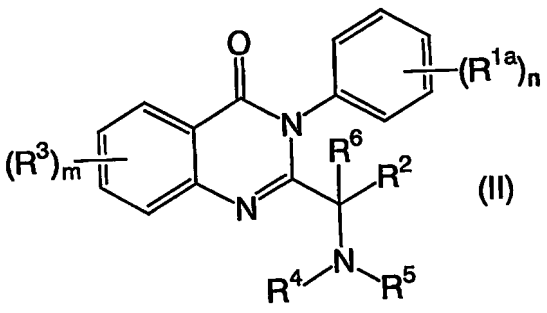
As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem. 11*:942-944).

B. Quinazolinone Modulators of Nuclear Receptors

Compounds for use in compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating farnesoid X receptor (FXR) and/or orphan nuclear receptors, are provided.

In one embodiment, the compounds have formula (I), where R^1 is hydrogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted aralkyl. In another embodiment, R^1 is hydrogen, optionally substituted alkyl, aryl, or aralkyl. In another embodiment, R^1 is hydrogen, methyl, ethyl, propyl, 2-methoxyethyl, benzyl, or naphthyl.

In one embodiment, the compounds for use in the compositions and methods provided herein have formula (I) where R^1 is optionally substituted phenyl. In another embodiment, the compounds have formula (II):



(II)

wherein:

n is an integer from 0 to 5;

m is an integer from 0 to 4;

each R^{1a} and R^3 are independently selected from halo, pseudohalo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-N(R^{12})R^{13}$, $-OR^{14}$, $-C(E)R^{15}$ where E is O, S or NR^7, or $-S(O)_yR^{16}$ where y is 0, 1 or 2, with the proviso that R^{1a} is not 3- or 4-$C(OH)(CF_3)_2$;

or any two R^{1a} groups or R^3 groups, which substitute adjacent carbons on the ring, together with atoms to which they are attached, form optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or optionally substituted aryl;

R^2, R^4, R^5 and R^6 are selected from (a) and (b) as follows:

(a) R^2 and R^6 are selected from (i) and (ii) as follows: (i) R^2 and R^6 are each independently hydrogen or optionally substituted alkyl; or (ii) R^2 and R^6 together form alkylene or alkenylene;

R^4 and R^5 are selected from (i) and (ii) as follows: (i) R^4 and R^5 are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-N(R^8)R^9$, $-OR^7$, $S(O)_jR^{11}$ where j is 1 or 2, $-B(R^{22})_2$, $-P(R^{22})_2$, $-P(O)(R^{22})_2$, and $-C(E)R^{23}$ where E is selected from O, S and NR^7; or (ii) R^4 and R^5 together form optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkyleneoxyalkylene or optionally substituted alkyleneazaalkylene;

(b) R^2 and R^5, or R^2 and R^4, or R^6 and R^5, or R^6 and R^4, together form a 5, 6 or 7 membered optionally substituted heterocyclyl group, or a 5 or 6 membered optionally substituted heteroaryl group; and the remainder of R^2, R^4,

R^5 and R^6 are each independently selected as in (i) above;

each R^7 is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, and optionally substituted heterocyclylalkyl;

R^8 and R^9 are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-S(O)_jR^{10}$ where j is 1 or 2, and $-C(M)R^{11}$, where M is selected from O and S;

or R^8 and R^9 together form alkylene, alkenylene, alkyleneoxyalkylene or alkyleneazaalkylene;

each R^{10} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, and optionally substituted heterocyclylalkyl;

each R^{11} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-OR^{10}$ and $-N(R^7)_2$;

R^{12} and R^{13} are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl,

optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-C(M)R^{17}$ where M is O or S, and $-S(O)_jR^{14}$ where j is 1 or 2;

or R^{12} and R^{13} together form alkylene, alkenylene, alkyleneoxyalkylene or alkyleneazaalkylene;

R^{14} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl or $-C(M)R^{17}$ where m is O or S;

R^{15} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, -OH, $-OR^{19}$ or $-N(R^{20})R^{21}$;

R^{16} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, -OH, $-OR^{19}$ or $-N(R^{20})R^{21}$;

R^{17} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-OR^{19}$ or $-N(R^{20})R^{21}$;

R^{18} is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-OR^{19}$ or $-N(R^{20})R^{21}$;

R^{19} is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl,

heterocyclylalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R^{20} and R^{21} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl,

or R^{20} and R^{21} together form alkylene, alkenylene or alkyleneoxyalkylene;

each R^{22} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-OR^7$ and $-N(R^7)_2$;

R^{23} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, $-OR^{10}$, $-N(R^7)_2$, $-N(R^7)N(R^7)_2$;

wherein each of the above R^1-R^{23} groups, when substituted, are substituted with one or more substituents each independently selected from Q^1, where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, carboxy, carboxyalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy,

alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^{+}(R^{24})_3$, $-P(R^{25})_2$, $-P(O)(R^{25})_2$, $-OP(O)(R^{25})_2$, $-N(R^{24})C(O)R^{26}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, carboxyalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_y-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_y-O-$) or alkylenedithioxy (*i.e.*, $-S-(CH_2)_y-S-$) where y is 1 or 2; or two Q^1 groups, which substitute the same atom, together form alkylene;

each R^{24} is independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl;

each R^{25} is independently selected from the group consisting of hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl and $-N(R^{27})R^{28}$,

R^{26} is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-N(R^{27})R^{28}$;

R^{27} and R^{28} are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl,

or R^{27} and R^{28} together form alkylene, azaalkylene, oxaalkylene or

thiaalkylene;

and each Q^1 is optionally substituted by one or more substituents selected from Q^2; where each Q^2 is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, carboxy, carboxyalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^+(R^{24})_3$, $-P(R^{25})_2$, $-P(O)(R^{25})_2$, $-OP(O)(R^{25})_2$, $-N(R^{24})C(O)R^{26}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, carboxyalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl,

alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^2 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-$(CH_2)_y$-O-), thioalkylenoxy (*i.e.*, -S-$(CH_2)_y$-O-) or alkylenedithioxy (*i.e.*, -S-$(CH_2)_y$-S-) where y is 1 or 2; or two Q^2 groups, which substitute the same atom, together form alkylene,

where R^{24}, R^{25}, R^{26}, R^{27} and R^{28} are as defined above;

as a stereoisomer, racemate or mixture thereof; or as a pharmaceutically acceptable derivative thereof.

In another embodiment, any two R^{1a} groups or R^3 groups, which substitute adjacent carbons on the ring, together with atoms to which they are attached, form optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkylenedioxy, optionally substituted thioalkylenoxy, or optionally substituted alkylenedithioxy.

In one embodiment, R^{1a} is not -C(OH)$(CF_3)_2$. In another embodiment, R^6 is hydrogen. In another embodiment, n is 0, 1 or 2. In another embodiment, m is 1.

In another embodiment, the compounds are of formula (II), where each R^{1a} is independently halo, pseudohalo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted dialkylamino, optionally substituted aralkoxy, hydroxy, optionally substituted heteroaryl, optionally substituted heterocyclyl or optionally substituted cycloalkyl.

In another embodiment, each R^{1a} is independently halo; pseudohalo; alkyl; haloalkyl; alkoxy; haloalkoxy; heterocyclylalkoxy; alkoxyalkoxy; aryl; aryl substituted with alkyl, halo, -C(O)OH, alkoxy, pseudohalo or -C(O)O-alkyl; dialkylamino; aralkoxy; hydroxy; heteroaryl; heterocyclyl; or cycloalkyl.

In another embodiment, each R^{1a} is independently chloro, fluoro, ethyl, methyl, methoxy, bromo, cyano, phenyl, *tert*-butyl, trifluoromethoxy, dimethylamino, trifluoromethyl, benzyloxy, hydroxy, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, ethoxy, isopropoxy, butoxy, isobutoxy, 2-(N-morpholino)ethoxy, 2-methoxyethoxy, 4-cyanophenyl, 2-thienyl, 3-thienyl, 3-methoxycarbonylphenyl, 4-

methoxycarbonylphenyl, 3-carboxyphenyl, *N*-pyrrolidinyl, or *N*-morpholinyl.

In another embodiment, R^2 is hydrogen or optionally substituted alkyl, and R^6 is hydrogen. In another embodiment, R^2 is hydrogen or alkyl. In another embodiment, R^2 is hydrogen, methyl or ethyl.

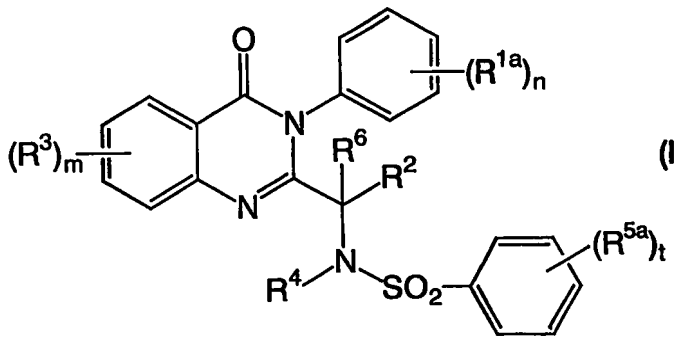
In another embodiment, each R^3 is independently optionally substituted alkyl, halo, pseudohalo, optionally substituted alkoxy, hydroxy, optionally substituted aralkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, or optionally substituted cycloalkyl.

In another embodiment, each R^3 is independently alkyl; halo; alkoxy; hydroxy; aralkoxy; aryl; heteroaryl; alkoxycarbonylalkoxy; aryl substituted with alkyl, halo, pseudohalo, alkoxy, -C(O)OH or -C(O)O-alkyl; or heterocyclyl.

In another embodiment, each R^3 is independently methyl, chloro, methoxy, hydroxy, bromo, ethoxy, isopropoxy, isobutoxy, butoxy, benzyloxy, ethoxycarbonylmethoxy, phenyl, 2-thienyl, 3-thienyl, 2-methylphenyl, 3-methylphenyl, 4-methylpheny, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-carboxyphenyl, *N*-pyrrolidinyl, *N*-morpholinyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 3-carboxyphenyl, 4-cyanophenyl, or piperidinyl.

In another embodiment, one of R^4 and R^5 is -SO_2-(optionally substituted aryl). In another embodiment, one of R^4 and R^5 is -SO_2-(optionally substituted phenyl).

In another embodiment, the compounds for use in the compositions and methods provided herein have formula (III):



(III)

where R^{1a}, R^2, R^3, R^4, R^6, n and m are as defined above; t is an integer from 0 to 5; each R^{5a} is independently optionally substituted alkyl, optionally substituted alkoxy,

optionally substituted heteroaryl, optionally substituted aryl, optionally substituted heterocyclyl, halo, pseudohalo; or any two R^{5a} substituents, which substitute adjacent atoms on the ring, together form a optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring having 5 or 6 members in the ring and where the heteroatoms, if present, are selected from O, S and optionally substituted N; where R^{5a}, when substituted, is substituted with one or more, in one embodiment one to five, in another embodiment one, two or three, substituents each independently selected from Q^1, as defined above.

In another embodiment, any two R^{5a} substituents, which substitute adjacent atoms on the ring, together form $-N=C(R^{29})-C(R^{29})=C(R^{29})-$ or $-C(R^{29})=C(R^{29})-C(R^{29})=C(R^{29})-$, where each R^{29} is independently hydrogen, halo, pseudohalo, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, or optionally substituted heteroaralkyl;

where R^{5a} and R^{29}, when substituted, are substituted with one or more, in one embodiment one to five, in another embodiment one, two or three, substituents each independently selected from Q^1, as defined above.

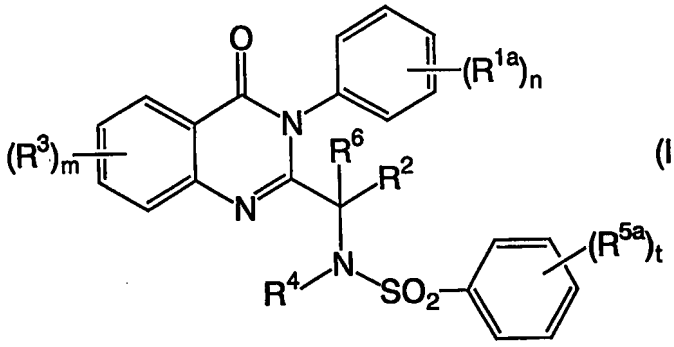
In another embodiment, the compounds have formula (III), where each R^{5a} is independently alkyl, alkoxy, haloalkoxy, heterocyclyl, heteroaryl, halo, haloalkyl, aryl or pseudohalo; or any two R^{5a} groups, which substitute adjacent carbons on the ring, together form -N=C(H)-C(H)=CH- or -C(H)=C(H)-C(H)=C(H)-.

In another embodiment, each R^{5a} is independently *tert*-butyl, methoxy, methyl, trifluoromethoxy, 2-thienyl, fluoro, chloro, trifluoromethyl, phenyl, cyano, *n*-propyl, 1,1-dimethylpropyl, isopropyl, butoxy or *n*-butyl; or any two R^{5a} groups, which substitute adjacent carbons on the ring, together form -N=C(H)-C(H)=CH- or -C(H)=C(H)-C(H)=C(H)-.

In another embodiment, the compounds have formula (III) where R^4 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, or optionally substituted heteroaralkyl. In another embodiment, R^4 is hydrogen, alkyl, aralkyl or heteroaralkyl. In another embodiment, R^4 is hydrogen, methyl, 2-methoxy-1-ethyl, propyl, isobutyl, butyl, pentyl, isopentyl, hexyl, benzyl, phenethyl or 2-thienylmethyl.

In another embodiment, one R^{5a} group is 4-*tert*-butyl or 4-isopropyl.

In another embodiment, the compounds of formula (II) are the compounds of formula (III):



(III)

wherein:

n is an integer from 0 to 5;

m is an integer from 0 to 4;

t is an integer from 0 to 5;

each R^{1a} is independently selected from the group consisting of alkyl, hydroxy, alkoxy, alkoxyalkoxy, aralkoxy, amino, alkylamino, dialkylamino, halo, haloalkyl, haloalkoxy, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkoxy, heteroaryl, heterocyclyl, heterocyclylalkoxy, and aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, cyano, carboxy, cyano, and alkoxycarbonyl);

R^2 is hydrogen or alkyl'

each R^3 is independently selected from the group consisting of alkyl, alkoxy, halo, hydroxy, aralkoxy, alkoxycarbonylalkoxy, aryl (optionally substituted by one or more substituents independently selected from the group consisting of alkyl, halo, alkoxy, carboxy, alkoxycarbonyl, cyano), heteroaryl and heterocyclyl;

R^4 is hydrogen or alkyl;

each R^{5a} is independently selected from the group consisting of alkyl, alkoxy, halo, alkylcarbonyl, haloalkyl, haloalkoxy, aryl, cyano, carboxy, alkoxycarbonyl, nitro, and $-N(R^{24})C(O)R^{26}$;

or two adjacent R^{5a} groups form an aryl, heterocyclyl or heteroaryl; and

R^6 is hydrogen or alkyl.

Of this group of compounds, a preferred subgroup are those

compounds wherein m is 0 or 1, n is 1 and each R^{1a} is alkoxy.

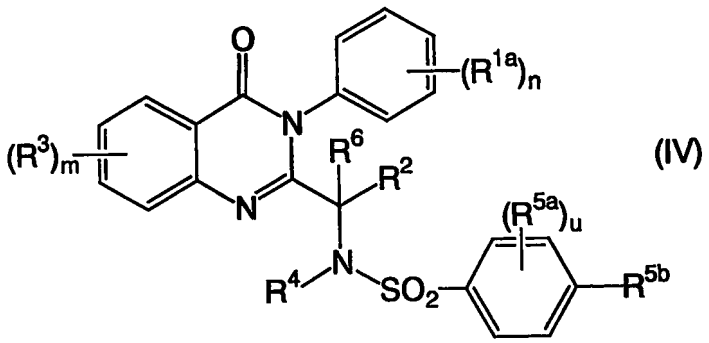
Another preferred subgroup are those compounds wherein m is 0 or 1, n is 1, 2 or 3 and each R^{1a} is selected from alkyl.

Another preferred subgroup are those compounds wherein m is 0 or 1, n is 1 and each R^{1a} is independently selected from halo, haloalkyl, haloalkoxy, and cyano.

Another preferred subgroup are those compounds wherein m is 0 or 1, n is 0 or 1 and each R^{1a} is selected from carboxy, dialkylamino, hydroxy, alkoxyalkoxy, alkoxycarbonylalkoxy, aralkoxy, and heterocyclylalkoxy.

Another preferred subgroup are those compounds wherein m is 0 or 1, n is 1 and R^{1a} is selected from optionally substituted aryl, heterocyclyl and heteroaryl. Even more preferred in this subgroup are those compounds wherein the aryl group is phenyl.

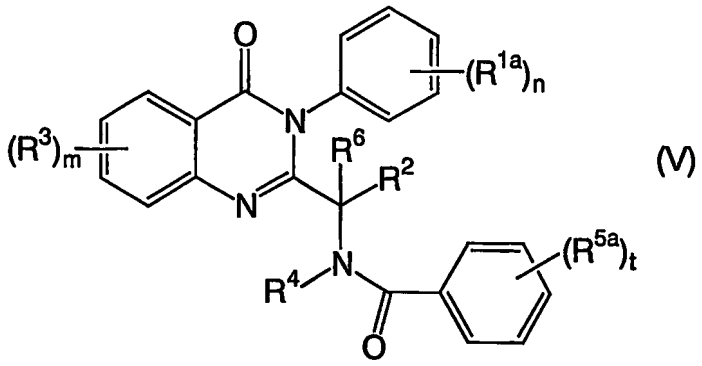
In another embodiment, the compounds for use in the compositions and methods provided herein have formula (IV):



(IV)

where R^{1a}, R^2, R^3, R^4, R^6, R^{5a}, m and n are selected as above; u is an integer from 0 to 4; and R^{5b} is *tert*-butyl or isopropyl. In another embodiment, R^{5b} is *tert*-butyl. In another embodiment, R^{5b} is isopropyl.

In another embodiment of formula (I), one of R^4 and R^5 is -C(O)-(optionally substituted aryl). In another embodiment, one of R^4 and R^5 is -C(O)-(optionally substituted phenyl). In another embodiment, the compounds for use in the compositions and methods provided herein have formula (V):



(V)

where R^{1a}, R^2, R^3, R^4, R^6, R^{5a}, t, n and m are as defined above.

In another embodiment, the compounds have formula (V) where each R^{1a} is independently halo, optionally substituted alkyl, or optionally substituted alkoxy, where the substituents, when present, are selected from Q^1, as defined above. In another embodiment, each R^{1a} is independently alkoxy, alkyl or halo. In another embodiment, each R^{1a} is independently methoxy, methyl, chloro or fluoro.

In another embodiment, the compounds have formula (V) where R^2 is hydrogen or optionally substituted alkyl, where the substituents, when present, are selected from Q^1, as defined above. In another embodiment, R^2 is hydrogen or alkyl. In another embodiment, R^2 is hydrogen or methyl.

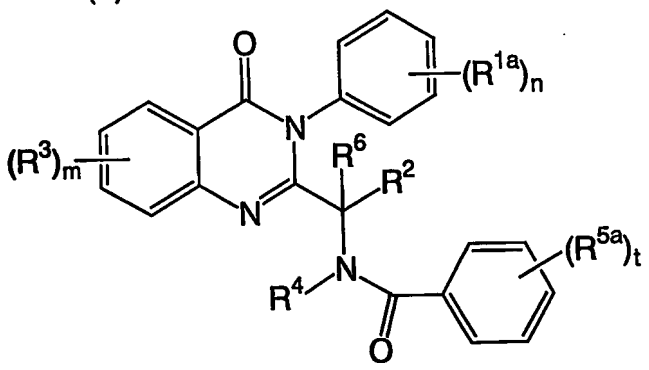
In another embodiment, the compounds have formula (V) where each R^3 is independently hydrogen or optionally substituted alkoxy, where the substituents, when present, are selected from Q^1, as defined above. In another embodiment, each R^3 is independently hydrogen or alkoxy. In another embodiment, each R^3 is independently hydrogen or methoxy.

In another embodiment, the compounds have formula (V) where R^4 is optionally substituted alkyl, where the substituents, when present, are selected from Q^1, as defined above. In another embodiment, R^4 is alkyl. In another embodiment, R^4 is butyl or methyl.

In another embodiment, the compounds have formula (V) where R^6 is hydrogen.

In another embodiment, the compounds have formula (V) where each R^{5a} is independently optionally substituted alkyl, where the substituents, when present, are selected from Q^1, as defined above. In another embodiment, each R^{5a} is alkyl. In another embodiment, R^{5a} is *tert*-butyl.

In another embodiment, the compounds of formula (II) are the compounds of formula (V):



(V)

wherein:

m is an integer from 0 to 4;

n is an integer from 0 to 5;

t is an integer from 0 to 5;

each R^{1a} is selected from the group consisting of alkyl, alkoxy, aralkoxy, halo, haloalkyl, haloalkoxy, amino, alkylamino, and dialkylamino;

R^2, R^4 and R^6 are each independently hydrogen or alkyl;

each R^3 is independently selected from the group consisting of alkyl, alkoxy, and halo; and

each R^{5a} is independently selected from the group consisting of alkyl, alkoxy, alkoxycarbonyl, halo, and aryl

or two adjacent R^{5a} groups form an aryl, heterocyclyl or heteroaryl.

Of this group of compounds, a preferred subgroup are those compounds wherein m is 0 or 1, n is 1 and each R^{1a} is alkoxy.

Another preferred subgroup are those compounds wherein m is 0 or 1, n is 1, 2 or 3 and each R^{1a} is selected from alkyl.

Another preferred subgroup are those compounds wherein m is 0 or 1, n is 0 or 1 and each R^{1a} is independently selected from dialkylamino, aralkoxy, halo, haloalkyl and haloalkoxy.

In another embodiment, the compounds have formula (I) where one of R^4 and R^5 is -C(O)-(optionally substituted alkyl), where the substituents, when present, are selected from Q^1, as defined above, and the other of R^4 and R^5 is selected from hydrogen and optionally substituted alkyl, where the substituents, when present, are

selected from Q^1, as defined above. In another embodiment, one of R^4 and R^5 is -C(O)-alkyl, and the other is alkyl. In another embodiment, one of R^4 and R^5 is -C(O)-octyl, and the other is methyl or butyl.

In another embodiment, the compounds have formula (I) where one of R^4 and R^5 is $-C(O)-N(R^8)R^9$, where R^8 and R^9 are independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkylalkyl, and optionally substituted heterocyclylalkyl; or R^8 and R^9 together form alkylene, alkenylene, alkyleneoxyalkylene or alkyleneazaalkylene; where R^8 and R^9 are each independently unsubstituted or substituted with one or more, in one embodiment one to five, in another embodiment one, two or three, substituents each independently selected from Q^1, as defined above, and the other of R^4 and R^5 is selected from hydrogen and optionally substituted alkyl, where the substituents, when present, are selected from Q^1, as defined above. In another embodiment, the other of R^4 and R^5 is alkyl. In another embodiment, the other of R^4 and R^5 is methyl or butyl.

In another embodiment, the compounds have formula (I) where R^8 and R^9 are each independently selected from hydrogen, optionally substituted cycloalkyl, and optionally substituted aryl. In another embodiment, R^8 is hydrogen. In another embodiment, R^9 is cyclohexyl, 4-nitrophenyl, 2-methoxyphenyl, 3-cyanophenyl, 3,4-dichlorophenyl, 2,6-diisopropylphenyl, 2-methylphenyl, 2-trifluoromethylphenyl, 2-fluorophenyl, 3-fluorophenyl, 3-methylphenyl, 3-chlorophenyl, 2,6-dimethylphenyl or 3-trifluoromethylphenyl.

In another embodiment, the compounds have formula (I) where R^4 and R^5 together form optionally substituted alkyleneazaalkylene, where the substituents, if present, are each independently selected from Q^1, as defined above. In one embodiment, there are one, two or three Q^1 substituents. In another embodiment, R^4 and R^5 together form $-CH_2-C(H)(Me)-N(R^{30})-CH_2-CH_2-$, where R^{30} is optionally substituted heteroarylcarbonyl, optionally substituted alkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted arylsulfonyl, optionally substituted

alkylaminocarbonyl, or optionally substituted arylaminocarbonyl.

In another embodiment, R^{30} is 2-thienylcarbonyl, butyryl, 4-fluorobenzoyl, benzyloxyacetyl, diphenylacetyl, 4-nitrobenzoyl, 2,5-dichlorobenzenesulfonyl, *tert*-butylaminocarbonyl, 4-*tert*-butylphenylsulfonyl, phenylaminocarbonyl, 2,3-dichlorophenylaminocarbonyl or 3,4-methylenedioxybenzoyl.

In another embodiment, the compounds for use in the compositions and methods provided herein have any of formulae I-V, where Q^2 is halo, pseudohalo, aralkoxy or nitro; or any two Q^2 groups, which substitute adjacent carbons, together form alkylenedioxy. In another embodiment, Q^2 is nitro, fluoro, benzyloxy or chloro; or two Q^2 groups, which substitute adjacent carbons, together form methylenedioxy.

Of the compounds disclosed herein, the most preferred compounds are those selected from the group consisting of the following:

4-*tert*-butyl-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide;

4-*tert*-butyl-*N*-{1-[6-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide;

4-*tert*-butyl-*N*-{1-[3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide;

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide;

4-*tert*-butyl-*N*-methyl-*N*-[1-(4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide;

4-*tert*-butyl-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide;

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-6-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide;

4-*tert*-butyl-*N*-{1-[6-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide;

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-isopropyl-*N*-methylbenzenesulfonamide; and

biphenyl-4-sulfonic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-

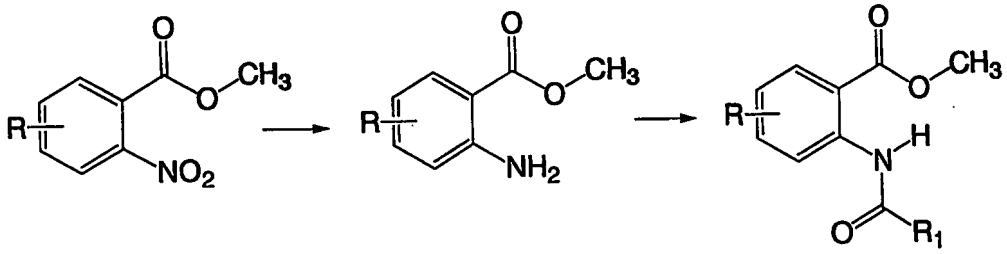
dihydroquinazolin-2-yl]ethyl}methylamide.

C. Preparation of the compounds

Starting materials in the synthesis examples provided herein are either available from commercial sources or *via* literature procedures. All commercially available compounds were used without further purification unless otherwise indicated. $CDCl_3$ (99.8% D, Cambridge Isotope Laboratories) was used in all experiments as indicated. Proton (^1H) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, and multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet). Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Low resolution mass spectra (MS) were obtained as electrospray ionization (ESI) mass spectra, which were recorded on a Perkin-Elmer SCIEX HPLC/MS instrument using reverse-phase conditions (acetonitrile/water, 0.05% trifluoroacetic acid). Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh) following standard protocol (Still *et al.* (1978) *J. Org. Chem. 43*, 2923).

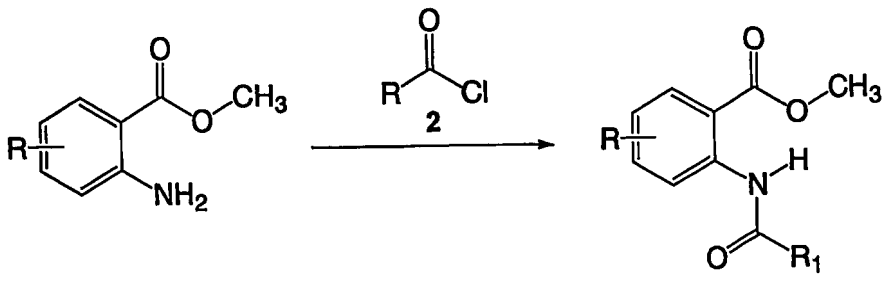
Substituted methyl-anthranilates are commercially available or can be synthetically obtained from commercially available starting materials, using standard literature protocols (Scheme 1) in which R is typically a halogen, alkyl, or alkoxy.

SCHEME 1



N-acyl methyl anthranilates **3** are prepared by treating methyl anthranilate **1** with an acid chloride **2** in which R_1 is typically alkyl, aryl, or heteroaryl (Scheme 2).

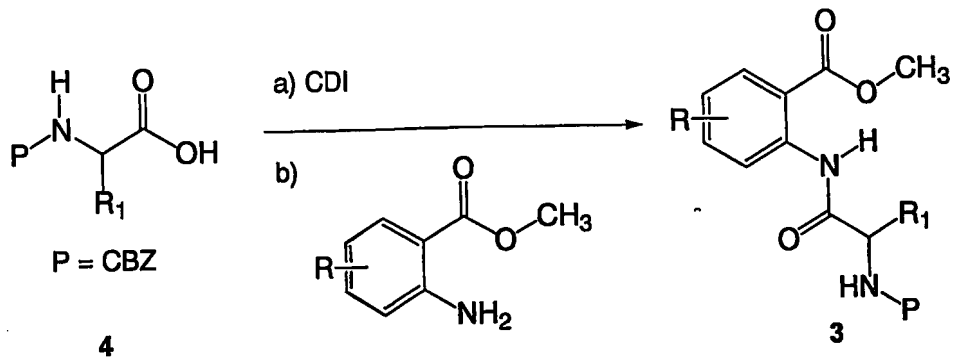
SCHEME 2



1 3

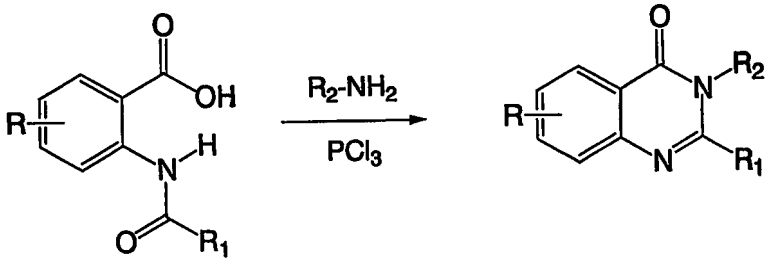
Acid chlorides are commercially available and/or can be prepared using standard methods found in literature. R_1 is typically 1-chloroethyl or a product derived from protected amino acids, *e.g.*, N-CBZ glycine. In the case where protected amino acids are used alternative acylation conditions were required (Yu, Melvin, *et al.* (1992) *J. Med. Chem. 35*:2534-2542). For example, the protected amino acid **4** is treated with carbonyl diimidazole (CDI) followed by subsequent treatment of a substituted methyl anthranilate **1** to yield the *N*-acyl methyl anthranilate **3** (Scheme 3). Once again, chemical diversity is realized by varying R and R_1 as previously described.

SCHEME 3



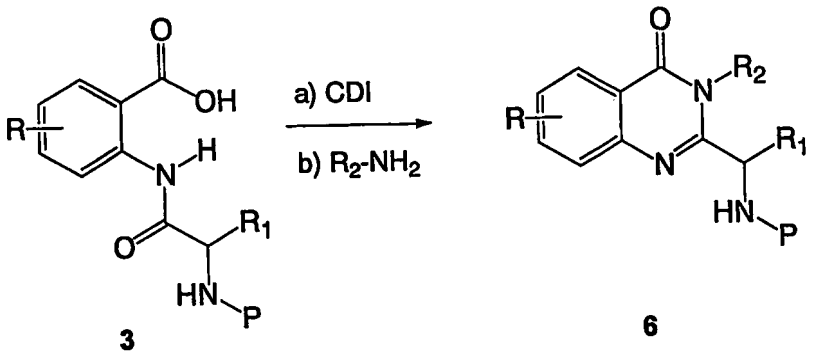
The quinazolinone core **5** was prepared by acylating an amine with the *N*-acyl anthranilic acid followed by a tandem cyclodehydration via thermolysis (Rao *et al.* (1985) *J. Indian Chem.*:234-237. *N*-Acyl anthranilic acid **3** was treated with phosphorous trichloride and an amine, under refluxing conditions, to afford the desired quinazolinones **5** (Scheme 4) in which R_2 typically includes an aryl (aniline), heteroaryl, or primary amines. When **3** possesses a protected amino appendage alternative conditions were required to generate the core (**6**)(Yu *et al.* (1992) *J. Med. Chem.* *35*:2534-2542).

SCHEME 4

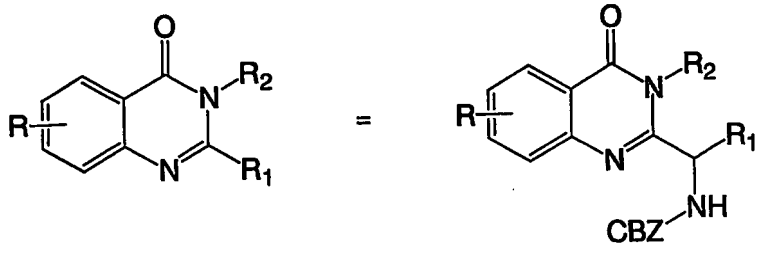


For example, compound **3** was treated with carbonyl diimidazole in which the resulting activated acid was treated with an amine (R_2-NH_2) under refluxing conditions to yield the quinazolinone **6** (Scheme 5).

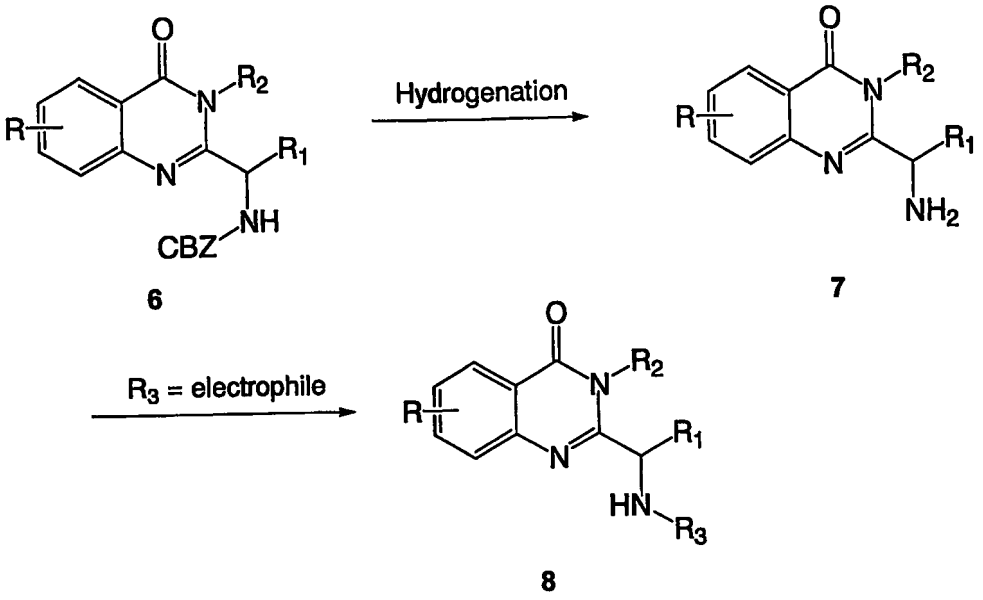
SCHEME 5



The protected amino appendage was then deprotected using standard conditions found in literature reference (Greene *et al. Protective Groups in Organic Synthesis*, 3rd Ed. (John Wiley, NY (1999))). For example, compound **5** was subjected to hydrogenation conditions to yield a free amine **7** (Scheme 6). Subsequently, the free amine was treated with a number of different electrophiles (R_3) to yield a diverse set of quinazolinone analogs (**8**) in which R_3 is typically an amide or sulfonamide but not limited to these groups. Additional electrophiles include carboxylic acids and derivatives thereof, sulfonyl chlorides, isocyanates, alkyl halides, aldehydes, ketones, and chloroformates.

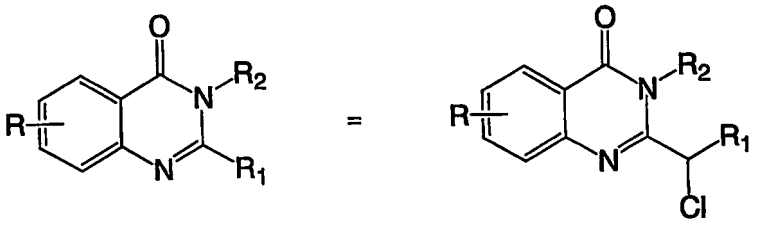


SCHEME 6



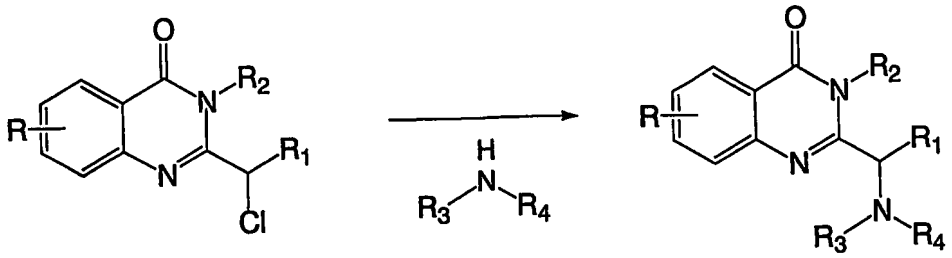
6 7 8

Alternatively, when R_1 is a substituted 1-chloroalkyl (**9**) various nucleophiles were introduced i.e. amines, alcohols, cuprates etc. For example when 1'-chloro ethyl quinazolinone **9** was treated with an amine under the appropriate conditions, quinazolinone **10** was realized (Scheme 7A). Subsequently, when R_4 is equal to hydrogen, **10** was treated with various electrophiles to yield compounds like **11**, in which R_4 is typically an amide or sulfonamide, but not limited to (Scheme 7B). Additional electrophiles include carboxylic acids and derivatives thereof, sulfonyl chlorides, isocyanates, alkyl halides, aldehydes, ketones, and chloroformates.



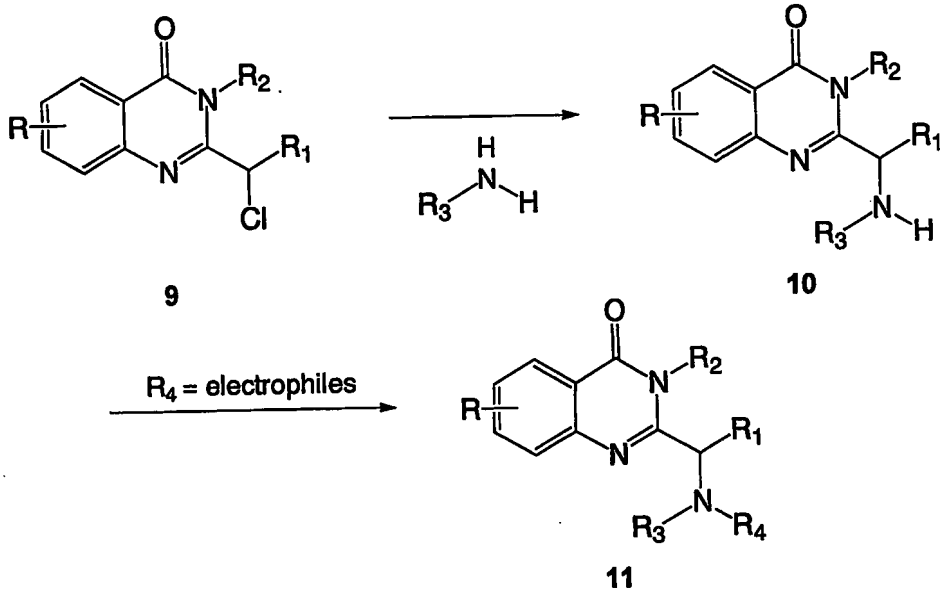
9

SCHEME 7A



9 10

SCHEME 7B

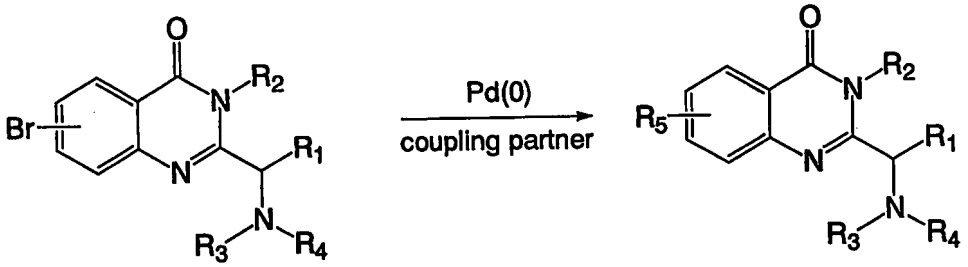


9 10 11

An aryl bromide containing quinazolinone (**12**) can be further manipulated with the addition of diverse structural modifications using standard C-C, C-N, and C-O bond forming reactions. The purpose of this was to gain entry into a diverse set of analogs that were not accessible through previously described methods. For example, a bromo-substituted heterocycle can be manipulated using standard transitions metal chemistries to introduce a large array of diverse functionalities that are otherwise difficult to obtain using alternative methods (Hegedus, Louis, S. *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books: Mill Valley, CA (1994)). Quinazolinone **12** was treated with Pd (0) and a phosphorous ligand in the presence of the appropriate coupling partner (R_5) to yield a

new series of quniazolinone analogs similar to **13** (Scheme 8). A typical (R_5) reagent would include boronic acids, (esters), amines, amides, mono-substituted alkynes, alcohols, or organotin reagents. These reagents are typically aryl, heteroaromatic, and alkyl in nature. In addition, these monomeric reagents are commercially available and/or can be synthesized using known literature methodologies.

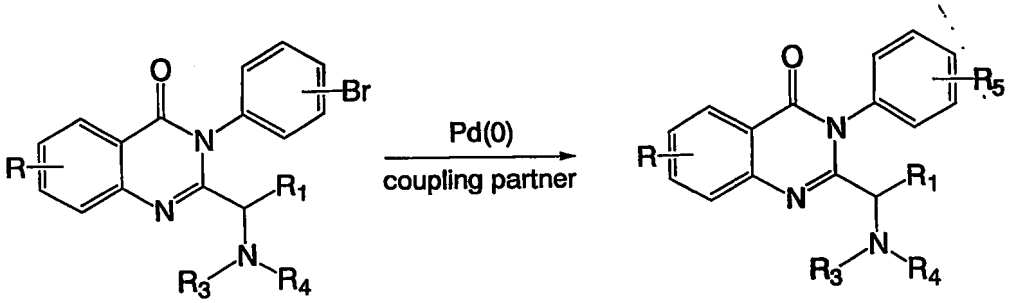
SCHEME 8



12 **13**

Similarly, compound **14** was modified using the same chemistries described above. The conditions and reagents used to modify the *N*-aryl quinazolinones **14** are identical to those previously described. Compound **14** was treated with Pd (0) and a phosphorous ligand in the presence of an appropriate monomer (R_5) to yield *N*-aryl substituted quinazolinones like compound **15** (Scheme 9). A typical (R_5) monomer would include boronic acids, amines, amides, mono-substituted alkynes, alcohols, or organotin reagents. These monomers are typically aryl, heteroaromatic, and alkyl in nature. In addition, these monomeric reagents are commercially available and/or can be synthesized using known literature methodologies.

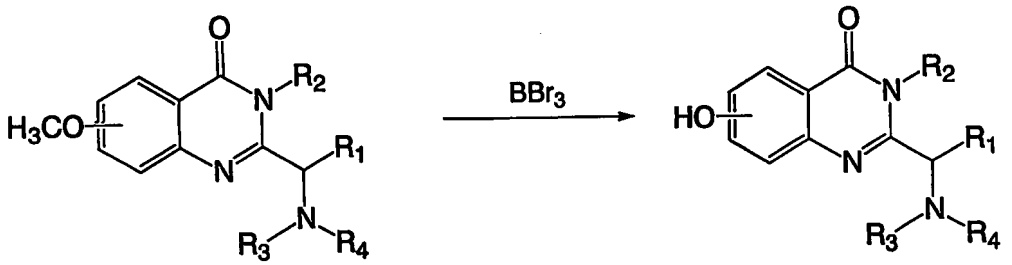
SCHEME 9



14 **15**

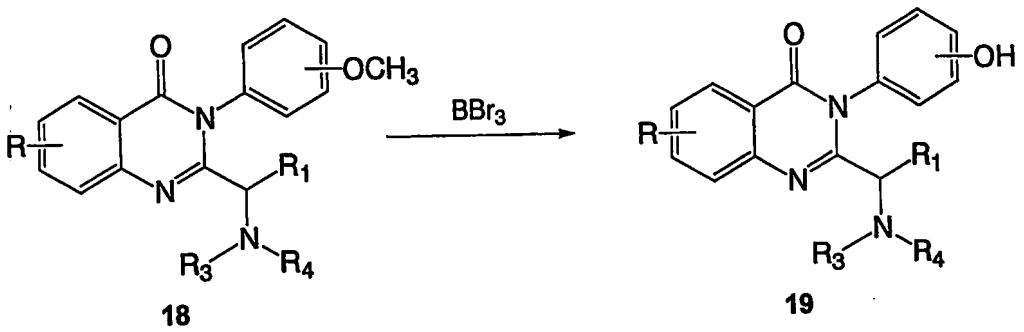
Additional modifications were made to the quinazolinone core by demethylating the methoxyphenyl ether of quinazolinone **16** to reveal a phenol **17** as handle for a point of diversity. Methoxy phenyl ethers are typically demethylated using a variety of literature methods (McOmie, J. F. W., West, D.E. *Org. Synth.*, Collect. Vol. V, 412 (1973): Jung, M. E., Lyster, M. A., *J. Org. Chem.*, **42**, 3761 (1977)). For example, when **16** is treated with boron tribromide the exclusive formation of phenol **17** was observed (Scheme 10). Similarly, the methoxy substituted N-aryl quinazolinone **18** was manipulated using the same protocol outlined above to yield compound **19** (Scheme 11).

SCHEME 10



16 **17**

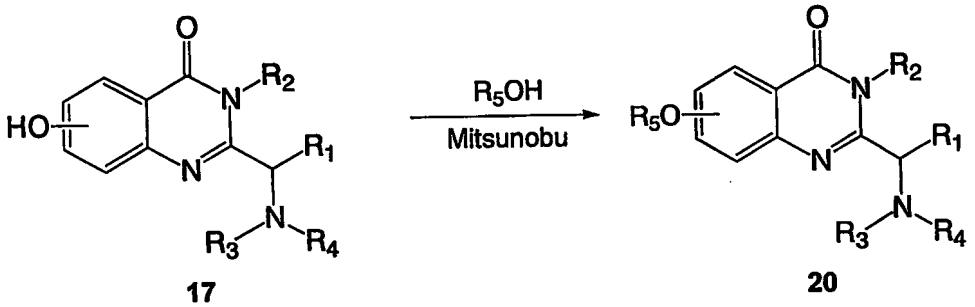
SCHEME 11



18 19

Treatment of a phenol with a variety of electrophiles establishes yet another avenue for diversity to be introduced that was not easily accessible with other methodologies. For example the phenol **17** was treated with various electrophiles, *i.e.* alkyl halides, isocyanates and acid chlorides to yield ethers, carbamates and esters respectively. Additionally, the phenol **17** was converted to various ethers **20** by utilizing the Mitsunobu reaction (Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.*, 1967, 40,2380; Canp, D.; Jenkins, I.D. *Aust. J. Chem.*, 1988, 41, 1835). Compound **17** was treated with triphenyl phosphine, alcohol (R_5OH) and diisopropyl azodicarboxylate (DIAD) to afford quinazolinone **20** (Scheme 12). Typical alcohols that were used include primary and secondary aliphatic alcohols. However, alcohols containing other functionalities were also used, *e.g.* ethyl glycolate.

SCHEME 12

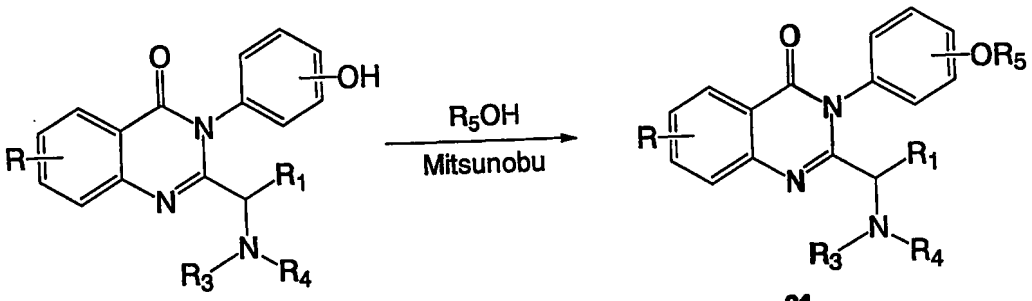


17 20

Similarly, compound **19** could be converted in an identical manner as described above to achieve analogs similar to **21**. A large array of diverse functionalities can be introduced that were otherwise difficult to obtain using alternative

methods (Scheme 13).

SCHEME 13



19 21

D. Formulation of pharmaceutical compositions

The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of the nuclear receptor activity modulators provided herein that are useful in the prevention, treatment, or amelioration of one or more of the symptoms of diseases or disorders associated with nuclear receptor activity, including FXR and/or orphan nuclear receptor activity. Such diseases or disorders include, but are not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

The compositions contain one or more compounds provided herein. The compounds are preferably formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the

art (see, *e.g.*, Ansel *Introduction to Pharmaceutical Dosage Forms, Fourth Edition* 1985, 126).

In the compositions, effective concentrations of one or more compounds or pharmaceutically acceptable derivatives is (are) mixed with a suitable pharmaceutical carrier or vehicle. The compounds may be derivatized as the corresponding salts, esters, enol ethers or esters, acids, bases, solvates, hydrates or prodrugs prior to formulation, as described above. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated. Such diseases or disorders include, but are not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients. Liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the

art. For example, liposome formulations may be prepared as described in U.S. Patent No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein and in International Patent Application Publication Nos. 99/27365 and 00/25134 (see, *e.g.*, EXAMPLES 15 and 16) and then extrapolated therefrom for dosages for humans.

The concentration of active compound in the pharmaceutical composition will depend on absorption, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated, as described herein.

Typically a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/ml to about 50-100 μg/ml. The pharmaceutical compositions typically should provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 1000 mg and preferably from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being

treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

Pharmaceutically acceptable derivatives include acids, bases, enol ethers and esters, salts, esters, hydrates, solvates and prodrug forms. The derivative is selected such that its pharmacokinetic properties are superior to the corresponding neutral compound.

Thus, effective concentrations or amounts of one or more of the compounds described herein or pharmaceutically acceptable derivatives thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. Compounds are included in an amount effective for ameliorating one or more symptoms of, or for treating or preventing diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated, as described herein. The concentration of active compound in the composition will depend on absorption, inactivation, excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

The compositions are intended to be administered by a suitable route, including orally, parenterally, rectally, topically and locally. For oral administration, capsules and tablets are presently preferred. The compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. Preferred modes of administration include parenteral and oral modes of administration. Oral administration is presently most preferred.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol,

glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The pharmaceutically therapeutically active compounds and derivatives thereof are typically formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes and individually

packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

The composition can contain along with the active ingredient: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum acacia gelatin, glucose, molasses, polvinylpyrrolidine, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity of the active compound in an amount sufficient to alleviate the symptoms of the treated subject.

Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum,

cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain 0.001%-100% active ingredient, preferably 0.1-85%, typically 75-95%.

The active compounds or pharmaceutically acceptable derivatives may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. The compositions may include other active compounds to obtain desired combinations of properties. The compounds provided herein, or pharmaceutically acceptable derivatives thereof as described herein, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated. It is to be understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

1. Compositions for oral administration

Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

In certain embodiments, the formulations are solid dosage forms,

preferably capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage

unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. The active ingredient is a compound or pharmaceutically acceptable derivative thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

Pharmaceutically acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets are compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film-coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar-coated, multiple compressed and chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a

preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic adds include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Patent Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to

be easily measured for administration.

Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. Re 28,819 and 4,358,603. Briefly, such formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

2. Injectables, solutions and emulsions

Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or

suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, *e.g.*, U.S. Patent No. 3,710,795) is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products,

such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired

pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

The unit-dose parenteral preparations are packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

Injectables are designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, preferably more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

3. Lyophilized powders

Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

The sterile, lyophilized powder is prepared by dissolving a compound provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbital, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, typically, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Generally, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage (10-1000 mg, preferably 100-500 mg) or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature.

Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, about 1-50 mg, preferably 5-35 mg, more preferably about 9-30 mg of lyophilized powder, is added per mL of sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

4. Topical administration

Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

The compounds or pharmaceutically acceptable derivatives thereof may

be formulated as aerosols for topical application, such as by inhalation (see, *e.g.*, U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns, preferably less than 10 microns.

The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7, with appropriate salts.

5. Compositions for other routes of administration

Other routes of administration, such as topical application, transdermal patches, and rectal administration are also contemplated herein.

For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared

either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 gm.

Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

6. Articles of manufacture

The compounds or pharmaceutically acceptable derivatives may be packaged as articles of manufacture containing packaging material, a compound or pharmaceutically acceptable derivative thereof provided herein, which is effective for modulating the activity of nuclear receptors, including FXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR and/or orphan nuclear receptor activity, is implicated, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including FXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR and/or orphan nuclear receptor activity, is implicated.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, *e.g.*, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any disease or disorder in which nuclear receptor activity, including FXR

and/or orphan nuclear receptor activity, is implicated as a mediator or contributor to the symptoms or cause.

E. Evaluation of the activity of the compounds

Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess biological activities that modulate the activity or nuclear receptors, including FXR and/or orphan nuclear receptors. Such assays include, for example, biochemical assays such as binding assays, fluorescence polarization assays, FRET based coactivator recruitment assays (see generally Glickman *et al.*, *J. Biomolecular Screening* (2002), Vol. 7, No. 1, pp. 3-10), as well as cell based assays including the co-transfection assay, the use of LBD-Gal 4 chimeras and protein-protein interaction assays (see, Lehmann, *et al.*, *J. Biol Chem.* (1997), Vol. 272, No. 6, pp. 3137-3140 (1997).

High throughput screening systems are commercially available (see, *e.g.*, Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments Inc., Fullerton, CA; Precision Systems, Inc., Natick, MA) that enable these assays to be run in a high throughput mode. These systems typically automate entire procedures, including all sample and reagent pipetting, liquid dispensing timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. These configurable systems provide high throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for various high throughput systems. Thus, for example, Zymark Corp. provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and the like.

Assays that do not require washing or liquid separation steps are preferred for such high throughput screening systems and include biochemical assays such as fluorescence polarization assays (see for example, Owicki, J., *Biomol. Screen* (2000), October, Vol. 5, No. 5, p. 297) scintillation proximity assays (SPA) (see, for example, Carpenter *et al.*, *Methods Mol. Biol.* (2002), Vol. 190, pp. 31-49) and fluorescence resonance energy transfer energy transfer (FRET) or time resolved FRET based coactivator recruitment assays (Mukherjee *et al.*, *J. Steroid Biochem. Mol. Biol.*

(2002), Vol. 81, No. 3, pp. 217-25; Zhou *et al.*, *Mol. Endocrinol.* (1998), Vol. 12, No. 10, pp. 1594-604). Generally such assays can be preformed using either the full length receptor, or isolated ligand binding domain (LBD). In the case of FXR, the LBD comprises amino acids 244 to 472 of the full length sequence.

If a fluorescently labeled ligand is available, fluorescence polarization assays provide a way of detecting binding of compounds to the nuclear receptor of interest by measuring changes in fluorescence polarization that occur as a result of the displacement of a trace amount of the label ligand by the compound. Additionally this approach can also be used to monitor the ligand dependent association of a fluorescently labeled coactivator peptide to the nuclear receptor of interest to detect ligand binding to the nuclear receptor of interest.

The ability of a compound to bind to a receptor, or heterodimer complex with RXR, can also be measured in a homogeneous assay format by assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor using a scintillation proximity assay (SPA). In this approach, the radioactivity emitted by a radiolabelled compound generates an optical signal when it is brought into close proximity to a scintillant such as a Ysi-copper containing bead, to which the nuclear receptor is bound. If the radiolabelled compound is displaced from the nuclear receptor the amount of light emitted from the nuclear receptor bound scintillant decreases, and this can be readily detected using standard microplate liquid scintillation plate readers such as, for example, a Wallac MicroBeta reader.

The heterodimerization of FXR with RXRα can also be measured by fluorescence resonance energy transfer (FRET), or time resolved FRET, to monitor the ability of the compounds provided herein to bind to FXR or other nuclear receptors. Both approaches rely upon the fact that energy transfer from a donor molecule to an acceptor molecule only occurs when donor and acceptor are in close proximity. Typically the purified LBD of the nuclear receptor of interest is labeled with biotin then mixed with stoichiometric amounts of europium labeled streptavidin (Wallac Inc.), and the purified LBD of RXRα is labeled with a suitable fluorophore such as CY5™. Equimolar amounts of each modified LBD are mixed together and allowed to equilibrate for at least 1 hour prior to addition to either variable or constant

concentrations of the sample for which the affinity is to be determined. After equilibration, the time-resolved fluorescent signal is quantitated using a fluorescent plate reader. The affinity of the compound can then be estimated from a plot of fluorescence versus concentration of compound added.

This approach can also be exploited to measure the ligand dependent interaction of a co-activator peptide with a nuclear receptor in order to characterize the agonist or antagonist activity of the compounds disclosed herein. Typically the assay in this case involves the use a recombinant Glutathione-S-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide sequenced derived from the receptor interacting domain of a co-activator peptide such as the steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

In the presence of an agonist for the nuclear receptor, the peptide is recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the allophycocyanin. Upon excitation of the complex with light at 340 nm excitation energy absorbed by the europium chelate is transmitted to the allophycocyanin moiety resulting in emission at 665 nm. If the europium chelate is not brought in to close proximity to the allophycocyanin moiety there is little or no energy transfer and excitation of the europium chelate results in emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an indication of the strength of the protein-protein interaction. The activity of a nuclear receptor antagonist can be measured by determining the ability of a compound to competitively inhibit (*i.e.*, IC_{50}) the activity of an agonist for the nuclear receptor.

In addition a variety of cell based assay methodologies may be successfully used in screening assays to identify and profile the specificity of compounds of the present invention. These approaches include the co-transfection assay, translocation assays, complementation assays and the use of gene activation technologies to over express endogenous nuclear receptors.

Three basic variants of the co-transfection assay strategy exist, co-

transfection assays using full-length nuclear receptor, co transfection assays using chimeric nuclear receptors comprising the ligand binding domain of the nuclear receptor of interest fused to a heterologous DNA binding domain, and assays based around the use of the mammalian two hybrid assay system.

The basic co-transfection assay is based on the co-transfection into the cell of an expression plasmid to express the nuclear receptor of interest in the cell with a reporter plasmid comprising a reporter gene whose expression is under the control of DNA sequence that is capable of interacting with that nuclear receptor. (See, for example, U.S. Patents Nos. 5,071,773; 5,298,429, 6,416,957, WO 00/76523). Treatment of the transfected cells with an agonist for the nuclear receptor increases the transcriptional activity of that receptor which is reflected by an increase in expression of the reporter gene, which may be measured by a variety of standard procedures.

For those receptors that function as heterodimers with RXR, such as FXR, the co-transfection assay typically includes the use of expression plasmids for both the nuclear receptor of interest and RXR. Typical co-transfection assays require access to the full length nuclear receptor and suitable response elements that provide sufficient screening sensitivity and specificity to the nuclear receptor of interest.

Genes encoding the following full-length previously described proteins, which are suitable for use in the co-transfection studies and profiling the compounds described herein, include rat FXR (GenBank Accession No. **NM_021745**), human FXR (GenBank Accession No. **NM_005123**), human RXR α (GenBank Accession No. **NM_002957**), human RXR β(GenBank Accession No. **XM_042579**), human RXR.γ (GenBank Accession No. **XM_053680**), human LXR α (GenBank Accession No. **NM_005693**), human LXR β (GenBank Accession No. **NM_007121**), human PPARα (GenBank Accession No. **NM_005036**) and human PPAR δ (GenBank Accession No. **NM_006238**).

Reporter plasmids may be constructed using standard molecular biological techniques by placing cDNA encoding for the reporter gene downstream from a suitable minimal promoter. For example luciferase reporter plasmids may be constructed by placing cDNA encoding firefly luciferase immediately down stream from

the herpes virus thymidine kinase promoter (located at nucleotides residues-105 to +51 of the thymidine kinase nucleotide sequence) which is linked in turn to the various response elements.

Numerous methods of co-transfecting the expression and reporter plasmids are known to those of skill in the art and may be used for the co-transfection assay to introduce the plasmids into a suitable cell type. Typically such a cell will not endogenously express nuclear receptors that interact with the response elements used in the reporter plasmid.

Numerous reporter gene systems are known in the art and include, for example, alkaline phosphatase Berger, J., *et al.* (1988) *Gene* 66 1-10; Kain, S.R. (1997) *Methods. Mol. Biol.* 63 49-60), β-galactosidase (See, U.S. Patent No. 5,070,012, issued Dec, 3, 1991 to Nolan *et al.*, and Bronstein, I., *et al.*, (1989) *J. Chemilum. Biolum.* 4 99-111), chloramphenicol acetyltransferase (See Gorman *et al.*, *Mol. Cell. Biol.* (1982) 2 1044-51), β-glucuronidase, peroxidase, β-lactamase (U.S. Patent Nos. 5,741,657 and 5,955,604), catalytic antibodies, luciferases (U.S. Patents 5,221,623; 5,683,888; 5,674,713; 5,650,289; 5,843,746) and naturally fluorescent proteins (Tsien, R.Y. (1998) *Annu. Rev. Biochem.* 67 509-44).

The use of chimeras comprising the ligand binding domain (LBD) of the nuclear receptor of interest to a heterologous DNA binding domain (DBD) expands the versatility of cell based assays by directing activation of the nuclear receptor in question to defined DNA binding elements recognized by defined DNA binding domain (see WO95/18380). This assay expands the utility of cell based co-transfection assays in cases where the biological response or screening window using the native DNA binding domain is not satisfactory.

In general the methodology is similar to that used with the basic co-transfection assay, except that a chimeric construct is used in place of the full length nuclear receptor. As with the full length nuclear receptor, treatment of the transfected cells with an agonist for the nuclear receptor LBD increases the transcriptional activity of the heterologous DNA binding domain which is reflected by an increase in expression of the reporter gene as described above. Typically for such chimeric constructs, the DNA binding domains from defined nuclear receptors, or from yeast or

bacterially derived transcriptional regulators such as members of the GAL 4 and Lex A / Umud super families are used.

A third cell based assay of utility for screening compounds of the present invention is a mammalian two-hybrid assay that measures the ability of the nuclear hormone receptor to interact with a cofactor in the presence of a ligand. (See for example, US Patent Nos. US 5,667,973, 5,283,173 and 5,468,614). The basic approach is to create three plasmid constructs that enable the interaction of the nuclear receptor with the interacting protein to be coupled to a transcriptional readout within a living cell. The first construct is an expression plasmid for expressing a fusion protein comprising the interacting protein, or a portion of that protein containing the interacting domain, fused to a GAL4 DNA binding domain. The second expression plasmid comprises DNA encoding the nuclear receptor of interest fused to a strong transcription activation domain such as VP16, and the third construct comprises the reporter plasmid comprising a reporter gene with a minimal promoter and GAL4 upstream activating sequences.

Once all three plasmids are introduced into a cell, the GAL4 DNA binding domain encoded in the first construct allows for specific binding of the fusion protein to GAL4 sites upstream of a minimal promoter. However because the GAL4 DNA binding domain typically has no strong transcriptional activation properties in isolation, expression of the reporter gene occurs only at a low level. In the presence of a ligand, the nuclear receptor-VP16 fusion protein can bind to the GAL4-interacting protein fusion protein bringing the strong transcriptional activator VP16 in close proximity to the GAL4 binding sites and minimal promoter region of the reporter gene. This interaction significantly enhances the transcription of the reporter gene, which can be measured for various reporter genes as described above. Transcription of the reporter gene is thus driven by the interaction of the interacting protein and nuclear receptor of interest in a ligand dependent fashion.

Any compound which is a candidate for activation of FXR may be tested by these methods. Generally, compounds are tested at several different concentrations to optimize the chances that activation of the receptor will be detected and recognized if present. Typically assays are performed in triplicate and vary within

experimental error by less than 15%. Each experiment is typically repeated three or more times with similar results.

Activity of the reporter gene can be conveniently normalized to the internal control and the data plotted as fold activation relative to untreated cells. A positive control compound (agonist) may be included along with DMSO as high and low controls for normalization of the assay data. Similarly, antagonist activity can be measured by determining the ability of a compound to competitively inhibit the activity of an agonist.

Additionally the compounds and compositions can be evaluated for their ability to increase or decrease the expression of genes known to be modulated by FXR and other nuclear receptors in vivo, using Northern-blot, RT PCR or oligonucleotide microarray analysis to analyze RNA levels. Western-blot analysis can be used to measure expression of proteins encoded by FXR target genes. Genes that are known to be regulated by the FXR include cholesterol 7 α-hydroxylase (CYP7A1), the rate limiting enzyme in the conversion of cholesterol to bile acids, the small heterodimer partner-1 (SHP-1), the bile salt export pump (BSEP, ABCB11), canalicular bile acid export protein, sodium taurocholate cotransporting polypeptide (NTCP, SLC10A1) and intestinal bile acid binding protein (I-BABP).

Established animal models exist for a number of diseases of direct relevance to the claimed compounds and these can be used to further profile and characterize the claimed compounds. These model systems include diabetic dislipidemia using Zucker (fa/fa) rats or (db/db) mice, spontaneous hyperlipidemia using apolipoprotein E deficient mice ($ApoE^{-/-}$), diet-induced hyperlipidemia, using low density lipoprotein receptor deficient mice ($LDR^{-/-}$) and atherosclerosis using both the Apo $E(^{-/-})$ and $LDL(^{-/-})$ mice fed a western diet. (21% fat, 0.05% cholesterol). Additionally FXR or LXR animal models (*e.g.*, knockout mice) can be used to further evaluate the present compounds and compositions in vivo (see, for example, Sinal, *et al.*, *Cell*, 102: 731-744 (2000), Peet, *et al.*, *Cell*, 93:693-704 (1998)).

F. Methods of use of the compounds and compositions

Methods of use of the compounds and compositions provided herein

are also provided. The methods involve both *in vitro* and *in vivo* uses of the compounds and compositions for altering nuclear receptor activity, including FXR and/or orphan nuclear receptor activity, and for treatment, prevention, or amelioration of one or more symptoms of diseases or disorder that are modulated by nuclear receptor activity, including FXR and/or orphan nuclear receptor activity, or in which nuclear receptor activity, including FXR and/or orphan nuclear receptor activity, is implicated.

Methods of altering nuclear receptor activity, including FXR, and/or orphan nuclear receptor activity, by contacting the receptor with one or more compounds or compositions provided herein, are provided.

Methods of reducing cholesterol levels and of modulating cholesterol metabolism, catabolism, absorption of dietary cholesterol (see, *e.g.*, International Patent Application Publication No. 00/40965) and reverse cholesterol transport (see, *e.g.*, International Patent Application Publication No. WO 00/78972), all of which implicate FXR activity, are provided. Also provided are methods of increasing the expression of ATP-Binding Cassette (ABC1) in mammalian cells using the compounds and compositions provided herein (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Methods of treatment, prevention, or amelioration of one or more symptoms of a disease or disorder affecting cholesterol, triglyceride, or bile acid levels are provided using the compounds and compositions provided herein. Also provided are methods of treatment, prevention, or amelioration of one or more symptoms of a disease or disorder affecting lipid metabolism (*i.e.*, lipodystrophy).

Methods of treatment, prevention, or amelioration of one or more forms of hyperlipidemia, including hypercholesterolemia (see, *e.g.*, International Patent Application Publication No. WO 00/57915); hyperlipoproteinemia (see, *e.g.*, International Patent Application Publication No. WO 01/60818) and hypertriglyceridemia are provided. The term "hyperlipidemia" refers to the presence of an abnormally elevated level of lipids in the blood. Hyperlipidemia can appear in at least three forms: (1) hypercholesterolemia, *i.e.*, an elevated cholesterol level; (2) hypertriglyceridemia, *i.e.*, an elevated triglyceride level; and (3) combined

hyperlipidemia, *i.e.*, a combination of hypercholesterolemia and hypertriglyceridemia.

Methods are also provided for the treatment, prevention, or amelioration of a number of disease states associated with elevated cholesterol levels, including coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma.

Methods of treatment, prevention, or amelioration of one or more symptoms of dyslipidemia are provided herein. The term "dyslipidemia" refers to abnormal levels of lipoproteins in blood plasma including both depressed and/or elevated levels of lipoproteins (*e.g.*, elevated levels of LDL, VLDL and depressed levels of HDL).

Methods of treatment, prevention, or amelioration of hyperglycemia or diabetes mellitus (see, *e.g.*, International Patent Application Publication No. WO 01/82917) are also provided using the compounds and compositions provided herein. Diabetes mellitus, commonly called diabetes, refers to a disease or condition that is generally characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels in the body (see, e.g., LeRoith, D. *et al.*, (eds.), *DIABETES MELLITUS* (Lippincott-Raven Publishers, Philadelphia, Pa. U.S.A. 1996)).

In the case of diabetes of the type 2 form, the disease is characterized by insulin resistance, in which insulin loses its ability to exert its biological effects across a broad range of concentrations. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver (see, *e.g.*, Reaven, G. M., *J. Basic & Clin. Phys. & Pharm.* (1998) 9: 387-406 and Flier, *J. Ann Rev. Med.* (1983) 34:145-60). The resulting condition is elevated blood glucose, which is called "hyperglycemia." Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for microvascular and macrovascular diseases, including retinopathy (the impairment or loss of vision due to blood vessel damage in the eyes); neuropathy (nerve damage and foot problems due to blood vessel damage to the nervous system); and nephropathy (kidney disease due to blood vessel damage in the

kidneys), hypertension, cerebrovascular disease and coronary heart disease. Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

Insulin resistance has been hypothesized to unify the clustering of hypertension, glucose intolerance, hyperinsulinemia, increased levels of triglyceride and decreased HDL cholesterol, and central and overall obesity. The association of insulin resistance with glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, hypertension, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plasminogen activator inhibitor-1, has been referred to as "Syndrome X" (see, *e.g.*, Reaven, G. M., *Physiol. Rev.* (1995) 75: 473-486). Accordingly, methods of treatment, prevention, or amelioration of any disorders related to insulin resistance including the cluster of disease states, conditions or disorders that make up "Syndrome X" are provided.

Methods of treatment, prevention, or amelioration of obesity, atherosclerosis, lipid disorders, cardiovascular disorders, or gallstone disease (see, *e.g.*, International Patent Application Publication No. WO 00/37077); acne vulgaris or acneiform skin conditions (see, *e.g.*, International Patent Application Publication No. WO 00/49992); Parkinson's disease, inflammation, immunological disorders, cancer or Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334); conditions characterized by a perturbed epidermal barrier function, peripheral occlusive disease, ischemic stroke, or conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. WO 98/32444) are provided.

Further provided herein are methods for the treatment, prevention, or amelioration of one or more symptoms of cholestasis, as well as for the treatment of the complications of cholestasis by administering a compound provided herein.

Cholestasis is typically caused by factors within the liver (intrahepatic) or outside the liver (extrahepatic) and leads to the accumulation of bile salts, bile pigment bilirubin, and lipids in the blood stream instead of being eliminated normally.

Intrahepatic cholestasis is characterized by widespread blockage of small ducts or by disorders, such as hepatitis, that impair the body's ability to eliminate bile. Intrahepatic cholestasis may also be caused by alcoholic liver disease, primary biliary cirrhosis, cancer that has spread (metastasized) from another part of the body, primary sclerosing cholangitis, gallstones, biliary colic and acute cholecystitis. It can also occur as a complication of surgery, serious injury, cystic fibrosis, infection, or intravenous feeding or be drug induced. Cholestasis may also occur as a complication of pregnancy and often develops during the second and third trimesters.

Extrahepatic cholestasis is most often caused by choledocholithiasis (Bile Duct Stones), benign biliary strictures (non-cancerous narrowing of the common duct), cholangiocarcinoma (ductal carcinoma) and pancreatic carcinoma. Extrahepatic cholestasis can occur as a side effect of many medications.

Accordingly, compounds provided herein may be used for the treatment, prevention, or amelioration of one or more symptoms of intrahepatic or extrahepatic cholestasis, including without limitation, biliary artesia, obstetric cholestasis, neonatal cholestasis, drug induced cholestasis, cholestasis arising from Hepatitis C infection, chronic cholestatic liver disease such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

Further provided by this invention are methods for treating obesity, as well as treating the complications of obesity, by administering a compound of the present invention. The terms "obese" and "obesity" refers to, according to the World Health Organization, a Body Mass Index (BMI) greater than 27.8 kg/m^2 for men and 27.3 kg/m^2 for women (BMI equals weight (kg)/height (m^2). Obesity is linked to a variety of medical conditions including diabetes and hyperlipidemia. Obesity is also a known risk factor for the development of type 2 diabetes (See, *e.g.*, Barrett-Conner, *E., Epidemol. Rev.* (1989) 11: 172-181; and Knowler, *et al., Am. J Clin. Nutr.* (1991) 53:1543-1551).

The compounds or composition that may be used for treating obesity or its complications, can be identified, formulated, and administered as previously described above. Such a compound or composition will comprise either a FXR selective antagonist a partial agonist/antagonist or antagonist that exhibits about a two

to about a ten-fold preference for FXR compared to another nuclear receptor such as, for example LXR α or β with respect to potency (IC_{50}, the concentration of compound that achieves 50% of the maximum reduction in the transcription activity achieved by the compound of interest observed in the presence of a sub-maximal concentration of FXR agonist) and/or efficacy (the maximum percent inhibition of transcription observed with the compound in question).

G. Combination Therapy

Also contemplated herein is combination therapy using a compound provided herein, or a pharmaceutically acceptable derivative thereof, in combination with one or more of the following: antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors (such as HMG CoA reductase inhibitors, such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin), acyl-coenzyme A:cholesterol acytransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants (such as anion exchange resins, or quaternary amines (*e.g.*, cholestyramine or colestipol)), low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B_6, vitamin B_{12}, anti-oxidant vitamins, β-blockers, anti-diabetes agents, angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, LXR α or β agonists, antagonists or partial agonists, aspirin or fibric acid derivatives. The compound provided herein, or pharmaceutically acceptable derivative thereof, is administered simultaneously with, prior to, or after administration of one or more of the above agents. Pharmaceutical compositions containing a compound provided herein and one or more of the above agents are also provided.

Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a FXR selective compound and one or more additional active agents, as well as administration of the FXR selective compound and each active agent in its own separate pharmaceutical dosage formulation. For example, a FXR agonist or antagonist of the present invention and an HMG-CoA reductase inhibitor can be administered to the patient together in a single oral dosage

composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, the compounds described herein and one or more additional active agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

The compound is preferably administered with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor. The term HMG-CoA reductase inhibitor is intended to include all pharmaceutically acceptable salt, ester, free acid and lactone forms of compounds which have HMG-CoA reductase inhibitory activity and, therefore, the use of such salts, esters, free acids and lactone forms is included within the scope of this invention. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified using assays well-known in the art. For instance, suitable assays are described or disclosed in U.S. Patent No. 4,231,938 and WO 84/02131. Examples of suitable HMG-CoA reductase inhibitors include, but are not limited to, lovastatin (MEVACOR®; see, U.S. Patent No. 4,231,938); simvastatin (ZOCOR®; see, U.S. Patent No. 4,444,784); pravastatin sodium (PRAVACHOL®; see, U.S. Patent No. 4,346,227); fluvastatin sodium (LESCOL®; see, U.S. Patent No. 5,354,772); atorvastatin calcium (LIPITOR®; see, U.S. Patent No. 5,273,995) and rivastatin (also known as cerivastatin; see, U.S. Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that can be used in the methods of the present invention are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs," *Chemistry & Industry*, pp. 85-89 (5 February 1996). In presently preferred embodiments, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

Dosage information for HMG-CoA reductase inhibitors is well known in the art, since several HMG-CoA reductase inhibitors are marketed in the U.S. In particular, the daily dosage amounts of the HMG-CoA reductase inhibitor may be the same or similar to those amounts which are employed for anti-hypercholesterolemic treatment and which are described in the Physicians' Desk Reference (PDR). For example, see the 50th Ed. of the PDR, 1996 (Medical Economics Co); in particular, see at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase

Inhibitors," and the reference pages cited therein. Preferably, the oral dosage amount of HMG-CoA reductase inhibitor is from about 1 to 200 mg/day and, more preferably, from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA reductase inhibitor which has sufficiently greater potency may be given in sub-milligram daily dosages.

As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg for lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; and for pravastatin sodium, 10 mg, 20 mg, and 40 mg. The daily dosage amount for atorvastatin calcium may be in the range of from 1 mg to 160 mg and, more particularly, from 5 mg to 80 mg. Oral administration may be in a single or divided doses of two, three, or four times daily, although a single daily dose of the HMG-CoA reductase inhibitor is preferred.

Diabetic patients are likely suffer from premature development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases. Hyperlipidemia and dyslipidemia are important precipitating factors for these diseases. Hyperlipidemia is a condition generally characterized by an abnormal increase in serum lipids (e.g. triglycerides and cholesterol) in the bloodstream and is an important risk factor in developing atherosclerosis and heart disease. See, e.g., Wilson, J. *et al.*, (ed.), Disorders of Lipid Metabolism, Chapter 23, *Textbook of Endocrinology*, 9th Edition, (W. B. Sanders Company, Philadelphia, Pa. U.S.A. 1998). Dyslipidemia is an abnormal levels of lipoproteins in blood plasma (e.g. elevated levels of LDL, VLDL and depressed levels of HDL), and has been shown to be one of the main contributors to the increased incidence of coronary events and deaths among diabetic subjects (see, e.g., Joslin, E. *Ann. Chim. Med.* (1927) 5: 1061-1079). Epidemiological studies since then have confirmed the association and have shown a several-fold increase in coronary deaths among diabetic subjects when compared with nondiabetic subjects (see, e.g., Garcia, M. J. *et al.*, *Diabetes* (1974) 23: 105-11 (1974); and Laakso, M. and Lehto, S., *Diabetes Reviews* (1997) 5(4): 294-315).

The methods of the present invention can be used effectively in combination with one or more additional active anti-diabetes agents depending on the

desired target therapy (see, e.g., Turner, N. et al., *Prog. Drug Res.* (1998) 51: 33-94; Haffner, S., *Diabetes Care* (1998) 21: 160-178; and DeFronzo, R. *et al.*, (eds.), *Diabetes Reviews* (1997) Vol. 5 No. 4). A number of studies have investigated the benefits of combination therapies with oral agents (see, *e.g.*, Mahler, R., *J. Clin. Endocrinol. Metab.* (1999) 84: 1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, *Diabetes Care* (1998) 21: 87-92; Bardin, C. W.,(ed.), CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM, 6th Edition (Mosby-Year Book, Inc., St. Louis, Mo. 1997); Chiasson, J. et al., *Ann. Intern. Med.* (1994) 121: 928-935; Coniff, R. *et al.*, *Clin. Ther.* (1997) 19: 16-26; Coniff, R. et al., *Am. J. Med.* (1995) 98: 443-451; and Iwamoto, Y. et al, *Diabet. Med.* (1996) 13 365-370; Kwiterovich, P. Am. *J. Cardiol* (1998) 82(12A): 3U-17U). These studies indicate that diabetes and hyperlipidemia modulation can be further improved by the addition of a second agent to the therapeutic regimen.

An example of combination therapy that modulates (prevents the onset of the symptoms or complications associated) atherosclerosis, is administered with one or more of the following active agents: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as β-sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrizol; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); vitamin B_3 (also known as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, such as vitamin C and E and beta carotene; a beta-blocker; LXR α or β agonists, antagonists, or partial agonists, an angiotensin II

antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin.

Still another example of combination therapy can be seen in modulating diabetes (or treating diabetes and its related symptoms, complications, and disorders) with, for example, sulfonylureas (such as chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, gliclazide, glynase, glimepiride, and glipizide), biguanides (such as metformin), thiazolidinediones (such as ciglitazone, pioglitazone, troglitazone, and rosiglitazone); and related insulin sensitizers, such as selective and non-selective activators of PPARα PPARβ and PPARγ; dehydroepiandrosterone (also referred to as DHEA or its conjugated sulphate ester, DHEA-SO_4); antiglucocorticoids; TNFα inhibitors; α-glucosidase inhibitors (such as acarbose, miglitol, and voglibose), pramlintide (a synthetic analog of the human hormone amylin), other insulin secretogogues (such as repaglinide, gliquidone, and nateglinide), insulin, as well as the active agents discussed above for treating atherosclerosis.

Another example of combination therapy is the co-administration of the compound or composition provided herein with compounds or composition for treating obesity or obesity-related disorders, wherein the methods can be effectively used in combination with, for example, phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine, dexfenfluramine, phentiramine, β_3 adrenoceptor agonist agents; sibutramine, gastrointestinal lipase inhibitors (such as orlistat), LXR α or β agonists, antagonists and partial agonists, and leptins. Other agents used in treating obesity or obesity-related disorders include neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine H_3 receptors, dopamine D_2 receptors, melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

Another example of a combination therapy can be seen in treating cholestasis, where the compounds of the invention can be combined with Actigall (Ursodeoxycholic acid - UDCA), corticosteroids, anti-infective agents (Rifampin, Rifadin, Rimactane), anti-viral agents, Vitamin D, Vitamin A, phenobarbital, cholestyramine, UV light, antihistamines, oral opiate receptor antagonists and

biphosphates, for the treatment, prevention, or amelioration of one or more symptoms of intrahepatic or extrahepatic cholestasis. Dosage information for these agents is well known in the art.

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention. Starting materials in the synthesis examples below are either available from commercial sources or via literature procedures. All commercially available compounds were used without further purification unless otherwise indicated. $CDCl_3$ (99.8% D, Cambridge Isotope Laboratories) was used in all experiments as indicated. Proton (^1H) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet). Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Low resolution mass spectra (MS) were obtained as electrospray ionization (ESI) mass spectra, which were recorded on a Perkin-Elmer SCIEX HPLC/MS instrument using reverse-phase conditions (acetonitrile/water, 0.05% trifluoroacetic acid). Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh) following standard protocol (Still et al. *J. Org. Chem.* **1978**, *43*, 2923).

EXAMPLE 1

PREPARATION OF 2-(2-CHLOROPROPIONYLAMINO)BENZOIC ACID METHYL ESTER AND RELATED COMPOUNDS

A. To methyl anthranilate (5 g, 33.1 mmol) stirring in DCM at 0°C under N_2 was added DIEA (5.1 g, 39.7 mmol) in one portion followed by the dropwise addition of 2-chloropropionyl chloride (4.2 g, 33.1 mmol). The reaction was allowed to stir at 0°C for 30 min. then warmed to room temperature, stirring for an additional 3 h. The reaction was treated with saturated aqueous solution of $NaHCO_3$ and the resulting biphasic mixture transferred to a separatory funnel. The layers separated and the aqueous layer was extracted twice more with DCM (25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum to

afford the desired product (7.75 g, 97% yield), which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 11.8 (br, 1H), 8.72 (dd, 1H), 8.08 (dd, 1H), 7.58 (m, 1H), 7.15 (m, 1H), 4.56 (q, 1H), 3.97 (s, 3H), 1.85 (d, 3H).

B. In a similar manner, but replacing methyl anthranilate with 2-amino-5-bromobenzoic acid methyl ester, the following compound was prepared:

5-bromo-2-(2-chloro-propionylamino)-benzoic acid methyl ester; ^{1}H-NMR ($CDCl_3$): δ 11.77 (broad, 1H), 8.64 (d, 1H), 8.18 (d, 1H), 7.65 (dd, 1H), 4.53 (q, 1H), 3.97 (s, 3H), 1.82 (d, 3H); MS (ESI) 320 (MH^+).

EXAMPLE 2

PREPARATION OF 2-(2-CHLOROPROPIONYLAMINO)BENZOIC ACID

To the 2-(2-chloro-propionylamino)-benzoic acid methyl ester (7.75 g, 32.1 mmol) stirring in THF (40 mL) was added 1M $LiOH/H_2O$ (40 mL). The reaction was allowed to stir at 50°C for 3 h. After this period the reaction was concentrated under vacuum to afford a crude residue that was acidified with 1N HCl. The resulting suspension was then diluted with EtOAc and washed with water (3 x 50 mL). The organic layer was then washed with brine (25 mL), dried over $MgSO_4$, and concentrated under vacuum to afford crude acid. The crude material was purified by flash chromatography (silica gel, 80% EtOAc/Hex) to afford the desired product as an off white solid (7.1 g, 97% yield). ^{1}H-NMR ($CDCl_3$): δ 8.6 (d, 1H), 8.12 (d, 1H), 7.61 (t, 1H), 7.57 (t, 1H), 4.89 (br, 1H), 4.65 (t, 1H), 1.78 (d, 3H).

EXAMPLE 3

PREPARATION OF 2-(1-CHLOROETHYL)-3-(4-METHOXYPHENYL)-3*H*-QUINAZOLIN-4-ONE AND RELATED COMPOUNDS

A. To a stirring suspension of 2-(2-chloropropionylamino)-benzoic acid (5 g, 22 mmol) and *p*-anisidine (2.7 g, 22 mmol) in 100 mL of toluene was added dropwise phosphorus trichloride (PCl_3) (3.02 g, 22 mmol) over 15 minutes. When the addition was complete the reaction was heated to reflux for 3 h and cooled to room

temperature and treated with 5 mL water. The resulting mixture was concentrated under vacuum to yield a semi-solid residue that was treated with 1N HCl and extracted twice with 200 mL portions of EtOAc. The organic extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated under vacuum to afford crude product that was purified by column chromatography (silica gel, EtOAc/Hex 4:1) (4.96 g, 72 % yield). ^{1}H-NMR ($CDCl_3$): δ 8.31 (m, 1H), 7.82 (m, 2H), 7.54 (m, 1H), 7.43 (dd, 1H), 7.09 (m, 3H), 4.66 (q, 1H), 3.91 (s, 3H), 1.89 (d, 3H).

B. In a similar manner, but replacing *p*-anisidine with the appropriate starting material, the following compounds were made:

2-(1-chloroethyl)-3-(4-methylphenyl)-3*H*-quinazolin-4-one; ^{1}H-NMR ($CDCl_3$): δ 8.29 (d, 1H), 7.80 (d, 2H), 7.52 (m, 1H), 7.38 (s, 2H), 7.34 (d, 1H), 7.07 (m, 1H), 4.62 (q, 1H), 2.46 (s, 3H), 1.87 (d, 3H); MS (ESI) 299 (MH^+);

3-(4-bromophenyl)-2-(1-chloroethyl)-3*H*-quinazolin-4-one; ^{1}H-NMR ($CDCl_3$): δ 8.28 (d, 1H), 7.81 (m, 2H), 7.70 (m, 2H), 7.54 (m, 1H), 7.39 (m, 1H), 7.08 (m, 1H), 4.55 (q, 1H), 1.88 (d, 3H); MS (ESI) 365 (MH^+); and

2-(1-chloroethyl)-3-(2,4-dimethylphenyl)-3*H*-quinazolin-4-one; ^{1}H-NMR ($CDCl_3$): δ 8.33 (d, 1H), 7.83 (m, 2H), 7.54 (m, 1H), 7.26 (m, 2H), 6.95 (d, 1H), 4.73 (q, 1H), 2.44 (s, 3H), 2.22 (s, 1.5H), 2.06 (s, 1.5H), 1.89 (m, 1H); MS (ESI) 313 (MH^+).

C. In a similar manner as described above in Paragraph A, but replacing 2-(2-chloropropionylamino)benzoic acid with 5-bromo-2-(2-chloro-propionylamino)benzoic acid and *p*-anisidine with 4-methyl-phenylamine, the following compound was prepared:

6-bromo-2-(1-chloroethyl)-3-*p*-tolyl-3*H*-quinolin-4-one; ^{1}H-NMR ($CDCl_3$): δ 8.40 (m, 1H), 7.87 (m, 1H), 7.67 (d, 1H), 7.37 (m, 3H), 7.04 (m, 1H), 4.59 (q, 1H), 2.46 (s, 3H), 1.84 (d, 3H); MS (ESI) 377 (MH^+).

EXAMPLE 4

PREPARATION OF [3-(4-METHOXYPHENYL)-4-OXO-3,4-DIHYDROQUINAZOLIN-2-YLMETHYL]-CARBAMIC ACID BENZYL ESTER AND RELATED COMPOUNDS

A. To a stirring suspension of 2-(2-benzyloxycarbonylamino-

acetylamino)-benzoic acid (2 g, 6.1 mmol) in THF (100 mL) was added carbonyldiimidizole (CDI) (1.0 g, 6.2 mmol) and stirred for 1h at room temperature under a nitrogen atmosphere. After 1h the reaction was treated with *p*-anisidine (0.73 g, 6.1 mmol) and refluxed for 16 h. The reaction was cooled to room temperature and concentrated under vacuum to afford a crude residue that was dissolved in EtOAc (50 mL). The mixture was then washed with saturated $NaHCO_3$ (50 mL) followed with brine (25 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford crude product that was purified by flash chromatography (silica gel, EtOAc/Hex 4:1) (1.21 g, 48 % yield). ^{1}H-NMR ($CDCl_3$): δ 8.26 (m, 1H), 7.72(m, 2H), 7.47 (m, 1H), 7.34 (m, 5H), 7.19 (m, 2H), 7.03 (m, 2H), 6.28 (broad, 1H), 5.10 (s, 2H), 4.50 (s, 2H), 3.85 (s, 3H).

B. In a similar manner, but replacing *p*-anisidine with 2,4-dimethylaniline, the following compound was made:

[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-carbamic acid benzyl ester; MS (ESI) 414 (MH^+).

EXAMPLE 5

PREPARATION OF 3-(4-METHOXYPHENYL)-2-(1-METHYLAMINOETHYL)-3*H*-QUINAZOLIN-4-ONE AND RELATED COMPOUNDS

A. To the neat 2-(1-chloroethyl)-3-(4-methoxyphenyl)-3*H*-quinazolin-4-one (1.0 g, 3.2 mmol) in a sealed tube was added 40 mL of a methylamine solution (1M in THF, 40 mmol). The tube was sealed and heated to 110°C 16 h. The resulting solution was cooled to room temperature and concentrated under vacuum to afford the crude product that was purified by flash chromatography (5% MeOH/DCM, silica gel) to afford the title compound (yield 0.97 g, 99%). ^{1}H-NMR (CD_3OD): δ 8.28 (m, 1H), 7.93 (m, 1H), 7.86 (m, 1H), 7.65 (m, 1H), 7.43 (m, 1H) 7.33 (m, 1H), 7.19 (m, 2H), 4.09 (q, 1H), 3.92 (s, 3H), 2.75 (s, 3H), 1.51 (d, 3H).

B. In a similar manner, but replacing 2-(1-chloroethyl)-3-(4-methoxyphenyl)-3*H*-quinazolin-4-one with the appropriate starting material, the following compounds were made:

2-(1-methylaminoethyl)-3-p-tolyl-3*H*-quinazolin-4-one; ^{1}H-NMR (CD_3OD): δ 8.28 (d, 1H), 7.77 (m, 1H), 7.71 (m, 1H), 7.47 (m, 1H), 7.36 (m, 2H), 7.12 (m, 2H), 3.37 (q, 1H), 2.46 (s, 3H), 2.28 (s, 3H), 1.24 (d, 3H); MS (ESI) 294 (MH^+);

6-bromo-2-(1-methylaminoethyl)-3-*p*-tolyl-3*H*-quinazolin-4-one; ^{1}H-NMR (CD_3OD): δ 8.39 (d, 1H), 7.84 (m, 1H), 7.59 (d, 1H), 7.37 (m, 2H), 7.11 (m, 2H), 3.36 (q, 1H), 2.46 (s, 3H), 2.26 (s, 3H), 1.57 (broad, 1H), 1.23 (d, 3H); MS (ESI) 317 (MH^+);

3-(2,4-dimethylphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one; ^{1}H-NMR (CD_3OD): δ 8.29 (d, 1H), 7.75 (m, 2H), 7.47 (t, 1H), 7.14 (s, 1H), 6.85 (d, 2H), 3.38 (q, 1H), 2.39 (s, 6H), 2.29 (s, 3H), 1.25 (d, 3H); MS (ESI) 308 (MH^+); and

3-(4-methoxyphenyl)-2-methylaminomethyl-3*H*-quinazolin-4-one; ^{1}H-NMR (CD_3OD): δ 8.27 (d, 1H), 7.93 (m, 1H), 7.86 (d, 1H), 7.65 (t, 1H), 7.43 (m, 1H), 7.33 (m, 1H), 7.19 (m, 2H), 4.08 (s, 2H), 3.92 (s, 3H), 2.74 (s, 3H); MS (ESI) 296 (MH^+).

C. In a similar manner, but with the appropriate starting materials, the following compound was made:

3-(4-methoxyphenyl)-8-methyl-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one; MS (ESI) 324 (MH^+).

D. In a similar manner as described above in Example 1, but replacing methyl anthranilate with the appropriate intermediate starting material, and in a similar manner as described above in Paragraph A, the following compounds were made:

3-(4-methoxyphenyl)-6-methyl-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one; MS (ESI) 324 (MH^+);

3-(4-methoxyphenyl)-7-methyl-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one; MS (ESI) 324 (MH^+);

8-methoxy-3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one; MS (ESI) 340 (MH^+);

5-methoxy-3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one; MS (ESI) 340 (MH^+); and

6-methoxy-3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one; MS (ESI) 340 (MH^+).

EXAMPLE 6

PREPARATION OF 2-AMINOMETHYL-3-(4-METHOXYPHENYL)-3*H*-QUINAZOLIN-4-ONE

In an oven dried flask that was purged with nitrogen was placed 3-(4-methyoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-carbamic acid benzyl ester (1.0 g, 2.4 mmol). The starting material was diluted with nitrogen sparged EtOH (25 mL) while maintaining a nitrogen atmosphere. To the reaction mixture was added 10% Pd/C (150 mg) and the reaction sealed with a septum. The sealed reaction was then purged with hydrogen by placing a syringe equipped with a balloon full of hydrogen gas through the septum. The reaction was stirred vigorously while inserting an additional needle in the septa to flush the atmosphere with hydrogen. With a full balloon of hydrogen in place the reaction was allowed to stir for 3 h after which it was concentrated under vacuum to yield crude material that was purified by flash chromatography (silica gel, 10% MeOH/DCM) (yield 0.67 g, 100 %). ^{1}H-NMR (CD_3OD): δ 8.23 (m, 1H), 7.87 (m, 1H), 7.80 (m, 1H), 7.56 (m, 1H), 7.13 (m, 2H), 7.01 (m, 2H), 3.90 (s, 3H), 3.51 (s, 2H); MS (ESI) 282 (MH^+).

EXAMPLE 7

PREPARATION OF 4-*TERT*-BUTYL-*N*-{1-[3-(4-METHOXYPHENYL)-4-OXO-3,4-DIHYDROQUINAZOLIN-2-YL]ETHYL}-*N*-METHYLBENZENESULFONAMIDE AND RELATED COMPOUNDS

A. To a suspension of the 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3H-quinazolin-4-one (50 mg, 0.16 mmol) stirring in 2 mL DCM was added TEA (19 mg, 0.19 mmol) followed by the addition of neat 4-*tert*-butyl-benzenesulfonyl chloride (37 mg, 0.16 mmol). The reaction was allowed to stir at room temperature for 2 h then treated with PS-tris-amine resin (100 mg). The reaction was allowed to stand for 15 min at room temperature after which the resin was removed by filtration. The filtrate was concentrated under vacuum to afford the crude product. The crude residue was purified by flash chromatography (silica gel, 50% EtOAc/Hex) to afford the desired product as an off-white powder (74 mg, 92 % yield). ^{1}H-NMR

($CDCl_3$): δ 8.15(d, 1H), 7.55 (s, 1H), 7.39 (m, 4H), 7.25 (d, 1H), 7.16 (m, 2H), 7.09 (m, 1H), 6.70 (m, 2H), 4.90 (q, 1H), 4.83 (s, 3H), 3.11 (s, 3H), 1.22 (d, 3H), 1.09 (s, 9H); MS (ESI) 506 (MH^+).

B. In a similar manner, but replacing 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one with the appropriate starting material, the following compounds were prepared:

4-*tert*-butyl-*N*-methyl-*N*-[1-(4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.22 (m, 1H), 7.63 (m, 1H), 7.51 (m, 2H), 7.44 (m, 3H), 7.33 (m, 2H), 7.23 (m, 2H), 7.06 (m, 1H), 4.95 (q, 1H), 3.19 (s, 3H), 2.48 (s, 3H), 1.30 (d, 3H), 1.16 (s, 9H); MS (ESI) 490 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; (mixture of rotomers) ^{1}H-NMR ($CDCl_3$): δ 8.30 (m, 1H), 7.72 (m, 1H), 7.56 (m, 4H), 7.38 (m, 2H), 7.30 (m, 2H), 7.21 (m, 1H), 5.03 (m, 1H), 3.15 (s, 1.5H), 3.01 (s, 1.5H), 2.47 (s, 1.5H), 2.45 (s, 1.5H), 2.26 (s, 1.5H), 2.04 (s, 1.5H), 1.31 (s, 4.5H), 1.24 (m, 3H), 1.21 (s, 4.5H); MS (ESI) 504 (MH^+);

4-*tert*-butyl-*N*-{1-[6-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 7.58 (d, 1H), 7.50 (d, 2H), 7.47 (m, 1H), 7.24 (m, 4H), 7.17 (m, 1H), 7.06 (m, 2H), 4.96 (q, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.15 (s, 3H), 1.28 (d, 3H), 1.18 (s, 9H); MS (ESI) 536 (MH^+);

4-*tert*-butyl-*N*-[1-(6-methoxy-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 7.58 (d, 1H), 7.50 (d, 2H), 7.44 (m, 1H), 7.34 (m, 1H), 7.24 (m, 5H), 7.05 (m, 1H), 4.93 (q, 1H), 3.88 (s, 3H), 3.15 (s, 3H), 2.48 (s, 3H), 1.28 (d, 3H), 1.18 (s, 9H); MS (ESI) 520 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-[1-(4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.22 (m, 1H), 7.63 (m, 1H), 7.51 (m, 2H), 7.44 (m, 3H), 7.33 (t, 2H), 7.22 (m, 2H), 7.06 (m, 1H), 4.95 (q, 1H), 3.19 (s, 3H), 2.48 (s, 3H), 1.30 (d, 3H), 1.16 (s, 9H); MS (ESI) 490 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-[1-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.25 (m, 1H), 7.76 (d, 2H), 7.52 (m, 1H), 7.45 (m, 3H), 5.53 (q, 1H), 3.84 (s, 3H), 2.81 (s, 3H), 1.41 (d, 3H), 1.27 (s, 9H);

MS (ESI) 414 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-[1-(4-oxo-3-p-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-benzamide; ^{1}H-NMR ($CDCl_3$): δ 8.28 (m, 1H), 7.76 (t, 1H), 7.69 (d, 1H), 7.48 (m, 2H), 7.36 (m, 4H), 7.28 (m, 1H), 7.19 (m, 1H), 6.96 (m, 1H), 5.43 (q, 1H), 3.10 (s, 3H), 2.41 (s, 3H), 1.49 (d, 3H), 1.31 (s, 9H); MS (ESI) 454 (MH^+); and

N-[1-(6-bromo-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-4-*tert*-butyl-*N*-methylbenzenesulfonamide; MS (ESI) 568 (MH^+).

C. In a similar manner as described above in Paragraph B, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-isopropyl-*N*-methylbenzenesulfonamide; (mixture of rotomers) ^{1}H-NMR ($CDCl_3$): δ 8.26 (m, 1H), 7.71 (m, 1H), 7.51 (m, 4H), 7.34 (m, 2H), 7.18 (m, 3H), 5.0 (m, 1H), 3.11 (s, 1.5H), 2.97 (s, 1.5H), 2.85 (m, 1H), 2.44 (s, 1.5H), 2.42 (s, 1.5H), 2.19 (s, 1.5H), 2.01 (s, 1.5H), 1.21 (m, 6H), 1.12 (m, 3H); MS (ESI) 490 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; (mixture of rotomers) ^{1}H-NMR ($CDCl_3$): δ 8.27 (m, 1H), 7.68 (m, 3H), 7.56 (m, 6H), 7.31 (m, 1H), 7.19 (m, 1H), 6.98 (m, 1H), 5.04 (m, 1H), 3.17 (s, 1.5H), 3.03 (s, 1.5H), 2.45 (s, 1.5H), 2.44 (s, 1.5H), 2.22 (s, 1.5H), 2.02 (s, 1.5H), 1.24 (m, 3H); MS (ESI) 524 (MH^+);

quinoline-8-sulfonic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; (mixture of rotomers) ^{1}H-NMR ($CDCl_3$): δ 8.56 (m, 1H), 8.49 (m, 0.5H), 8.34 (m, 1H), 8.19 (m, 1H), 7.97 (m, 1H), 7.89 (m, 0.5H), 7.77 (m, 1H), 7.54 (m, 3H), 7.40 (m, 1H), 7.31 (m, 1H), 7.22 (m, 1H), 7.10 (m, 1H), 5.66 (m, 1H), 3.32 (s, 3H), 2.48 (m, 3H), 2.10 (m, 3H), 1.18 (m, 3H); MS (ESI) 499 (MH^+);

N-[1-(6-bromo-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-4-isopropyl-*N*-methylbenzenesulfonamide; MS (ESI) 554 (MH^+);

biphenyl-4-sulfonic acid [1-(6-bromo-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]methylamide; MS (ESI) 588 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid [1-(6-bromo-4-oxo-3-*p*-tolyl-3,4-

dihydroquinazolin-2-yl)ethyl]methylamide; MS (ESI) 520 (MH^+); and

N-[1-(6-bromo-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-4-*tert*-butyl-*N*-methylbenzamide; MS (ESI) 532 (MH^+).

D. In a similar manner as described above in Paragraph A, but replacing 4-*tert*-buylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

nonanoic acid {1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 450 (MH^+);

4-methoxy-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 444 (MH^+);

4-methoxy-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 480 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 458 (MH^+);

N-{1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-terephthalamic acid methyl ester; MS (ESI) 472 (MH^+);

2-methoxy-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 444 (MH^+);

3-methoxy-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 444 (MH^+);

N-{1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 464 (MH^+); and

4-cyano-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 475 (MH^+).

E. 4-Cyano-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide, prepared as described above in Paragraph D, was hydrolyzed with concentrated HCl at reflux to yield 4-({1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-methyl-sulfamoyl)-benzoic acid; MS (ESI) 494 (MH^+).

F. In a similar manner as described above in Paragraph A, but replacing 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3H-quinazolin-4-one with 2-(1-

methylaminoethyl)-3-*p*-tolyl-3*H*-quinazolin-4-one and 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

benzo[1,3]dioxole-5-carboxylic acid methyl-[1-(4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]amide; MS (ESI) 442 (MH^+);

4-isopropyl-*N*-methyl-*N*-[1-(4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 476 (MH^+); and

biphenyl-4-sulfonic acid methyl-[1-(4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]amide; MS (ESI) 510 (MH^+).

G. In a similar manner as described above in Paragraph A, but replacing 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3H-quinazolin-4-one with 2-aminomethyl-3-(4-methoxyphenyl)-3*H*-quinazolin-4-one and 4-*tert*-butyl-benzenesulfonyl chloride with *p*-toluenesulfonyl chloride, the following compound was made:

N-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-4-methylbenzenesulfonamide; MS (ESI) 436 (MH^+).

H. In a similar manner as described above in Paragraph G, but replacing *p*-toluenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-*tert*-butyl-*N*-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzenesulfonamide; MS (ESI) 478 (MH^+);

N-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzamide; MS (ESI) 386 (MH^+);

4-chloro-*N*-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzamide; MS (ESI) 420 (MH^+);

3-methoxy-*N*-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzamide; MS (ESI) 416 (MH^+);

4-methoxy-*N*-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzamide; MS (ESI) 416 (MH^+);

4-*tert*-butyl-*N*-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzamide; MS (ESI) 442 (MH^+);

N-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-

terephthalamic acid methyl ester; MS (ESI) 444 (MH^+);

2,4-dichloro-*N*-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzamide; MS (ESI) 454 (MH^+);

4-methoxy-*N*-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzenesulfonamide; MS (ESI) 452 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid [3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]amide; MS (ESI) 430 (MH^+);

nonanoic acid [3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]amide; MS (ESI) 422 (MH^+); and

4-chloro-*N*-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzenesulfonamide; MS (ESI) 456 (MH^+).

I. [3-(2,4-Dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]carbamic acid benzyl ester, as prepared above in Example 4, was hydrogenated in a similar manner as described above in Example 6, and then condensed, as described above in Paragraph A, with benzenesulfonyl chloride to yield *N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzenesulfonamide; MS (ESI) 420 (MH^+).

J. In a similar manner as described above in Paragraph I, but replacing benzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-4-methylbenzenesulfonamide; MS (ESI) 434 (MH^+);

4-*tert*-butyl-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzenesulfonamide; MS (ESI) 476 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-4-methoxy-benzenesulfonamide; MS (ESI) 450 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzamide; MS (ESI) 384 (MH^+);

4-*tert*-butyl-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzamide; MS (ESI) 440 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-

dihydroquinazolin-2-ylmethyl]amide; MS (ESI) 428 (MH^+);

2,4-dichloro-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]benzamide; MS (ESI) 452 (MH^+); and

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-terephthalamic acid methyl ester; MS (ESI) 442 (MH^+).

K. In a similar manner as described above in Paragraph A, but replacing 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one with 3-(2,4-dimethylphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one and replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-methoxy-*N*-methylbenzenesulfonamide; MS (ESI) 478 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 456 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-terephthalamic acid methyl ester; MS (ESI) 470 (MH^+);

naphthalene-1-sulfonic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 498 (MH^+);

naphthalene-2-sulfonic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 498 (MH^+);

2-naphthalen-1-yl-ethanesulfonic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 526 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-2,*N*-dimethylbenzenesulfonamide; MS (ESI) 462 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-3,*N*-dimethylbenzenesulfonamide; MS (ESI) 462 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 462 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-C-phenyl-methanesulfonamide; MS (ESI) 462 (MH^+);

4-acetyl-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-

yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 490 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-3-trifluoromethylbenzenesulfonamide; MS (ESI) 516 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-4-trifluoromethoxy-benzenesulfonamide; MS (ESI) 532 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-2,5,*N*-trimethylbenzenesulfonamide; MS (ESI) 476 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-3,4-dimethoxy-*N*-methylbenzenesulfonamide; MS (ESI) 508 (MH^+);

N-[4-({1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-methyl-sulfamoyl)-phenyl]-acetamide; MS (ESI) 505 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-2,4,6,*N*-tetramethylbenzenesulfonamide; MS (ESI) 490 (MH^+);

2-phenyl-ethenesulfonic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 474 (MH^+);

2,2,5,6,8-pentamethyl-chroman-7-sulfonic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 574 (MH^+);

thiophene-2-sulfonic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 454 (MH^+);

C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-methanesulfonamide; MS (ESI) 522 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-3,4-difluoro-*N*-methylbenzenesulfonamide; MS (ESI) 484 (MH^+);

3-chloro-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-2,*N*-dimethylbenzenesulfonamide; MS (ESI) 496 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-5-fluoro-2,*N*-dimethylbenzenesulfonamide; MS (ESI) 480 (MH^+);

3,5-dimethyl-isoxazole-4-sulfonic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 467 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-4-trifluoromethylbenzenesulfonamide; MS (ESI) 516 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-3-fluoro-*N*-methylbenzenesulfonamide; MS (ESI) 466 (MH^+);

2,4,6-trichloro-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 550 (MH^+);

3-chloro-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-fluoro-*N*-methylbenzenesulfonamide; MS (ESI) 500 (MH^+);

2-chloro-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 482 (MH^+);

5-chloro-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-2-methoxy-*N*-methylbenzenesulfonamide; MS (ESI) 512 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-2,5-dimethoxy-*N*-methylbenzenesulfonamide; MS (ESI) 508 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-2,3,4-trifluoro-*N*-methylbenzenesulfonamide; MS (ESI) 502 (MH^+);

3-chloro-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 482 (MH^+);

4-cyano-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 473 (MH^+);

4-butyl-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 504 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-(1,1-dimethyl-propyl)-*N*-methylbenzenesulfonamide; MS (ESI) 518 (MH^+);

4-butoxy-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 520 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-3-methoxy-*N*-methylbenzenesulfonamide; MS (ESI) 478 (MH^+);

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-2-methoxy-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 492 (MH^+);

4-chloro-*N*-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-

yl]ethyl}-2,5,*N*-trimethylbenzenesulfonamide; MS (ESI) 510 (MH^+); and

N-{1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-methanesulfonamide; MS (ESI) 386 (MH^+).

L. In a similar manner as described above in Paragraph A, but replacing 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one with 3-methyl-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one and replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-isopropyl-*N*-methyl-*N*-[1-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 400 (MH^+);

biphenyl-4-sulfonic acid methyl-[1-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl]amide; MS (ESI) 434 (MH^+);

4-methoxy-*N*-methyl-*N*-[1-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 388 (MH^+); and

4-chloro-*N*-methyl-*N*-[1-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 392 (MH^+).

M. In a similar manner as described above, 3-(4-methoxyphenyl)-8-methyl-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one, as prepared above in Example 5, was condensed with 4-*tert*-butylbenzenesulfonyl chloride to yield 4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-8-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 520 (MH^+).

N. In a similar manner as described above in Paragraph M, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-isopropyl-*N*-{1-[3-(4-methoxyphenyl)-8-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 506 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(4-methoxyphenyl)-8-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 540 (MH^+);

N-{1-[3-(4-methoxyphenyl)-8-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 478 (MH^+);

4-methoxy-*N*-{1-[3-(4-methoxyphenyl)-8-methyl-4-oxo-3,4-

dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 494 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(4-methoxyphenyl)-8-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 472 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-8-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 484 (MH^+);

4-butyl-*N*-{1-[3-(4-methoxyphenyl)-8-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 520 (MH^+);

N-{1-[3-(4-methoxyphenyl)-8-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-4-trifluoromethylbenzenesulfonamide; MS (ESI) 532 (MH^+); and

2,4,6-trichloro-*N*-{1-[3-(4-methoxyphenyl)-8-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 566 (MH^+).

O. In a similar manner as described above in Paragraph M, but replacing 2-amino-3-methylbenzoic acid as an intermediate starting material in a prior step with 2-amino-6-methylbenzoic acid, the following compound was made:

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 520 (MH^+).

P. In a similar manner as described above in Paragraph O, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-isopropyl-*N*-{1-[3-(4-methoxyphenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 506 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(4-methoxyphenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 540 (MH^+);

N-{1-[3-(4-methoxyphenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 478 (MH^+);

4-methoxy-*N*-{1-[3-(4-methoxyphenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 494 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(4-methoxyphenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 472 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 484 (MH^+);

4-butyl-*N*-{1-[3-(4-methoxyphenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 520 (MH^+);

N-{1-[3-(4-methoxyphenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-4-trifluoromethylbenzenesulfonamide; MS (ESI) 532 (MH^+); and

2,4,6-trichloro-*N*-{1-[3-(4-methoxyphenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 566 (MH^+).

Q. In a similar manner as described above in Paragraph M, but replacing 2-amino-3-methylbenzoic acid as an intermediate starting material in a prior step wih 2-amino-4-chlorobenzoic acid, the following compound was made:

4-*tert*-butyl-*N*-{1-[7-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 541 (MH^+).

R. In a similar manner as described above in Paragraph Q, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

N-{1-[7-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-isopropyl-*N*-methylbenzenesulfonamide; MS (ESI) 526 (MH^+);

biphenyl-4-sulfonic acid {1-[7-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 560 (MH^+);

N-{1-[7-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-methoxy-*N*-methylbenzenesulfonamide; MS (ESI) 514 (MH^+);

N-{1-[7-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 484 (MH^+);

N-{1-[7-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 498 (MH^+);

N-{1-[7-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-4-trifluoromethylbenzenesulfonamide; MS (ESI) 552 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[7-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 492 (MH^+); and

4-*tert*-butyl-*N*-{1-[7-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 504 (MH^+).

S. In a similar manner as described above in Paragraph M, but

replacing 2-amino-3-methylbenzoic acid as an intermediate starting material in a prior step wih the appropriate intermediate starting material, the following compounds were made:

4-*tert*-butyl-*N*-{1-[6-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 540 (MH^+); and

4-*tert*-butyl-*N*-{1-[8-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 540 (MH^+).

T. In a similar manner as described above in Paragraph S, but replacing 4-*tert*-butylbenzenesulfonyl chloride, the following compounds were made:

N-{1-[6-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-isopropyl-*N*-methylbenzenesulfonamide; MS (ESI) 526 (MH^+);

biphenyl-4-sulfonic acid {1-[6-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 560 (MH^+);

N-{1-[6-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-methoxy-*N*-methylbenzenesulfonamide; MS (ESI) 514 (MH^+);

N-{1-[6-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 484 (MH^+);

N-{1-[6-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 498 (MH^+);

N-{1-[6-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-4-trifluoromethylbenzenesulfonamide; MS (ESI) 552 (MH^+);

2,4,6-trichloro-*N*-{1-[6-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 586 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[6-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 492 (MH^+);

4-*tert*-butyl-*N*-{1-[6-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 504 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[8-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 492 (MH^+);

4-*tert*-butyl-*N*-{1-[8-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 504 (MH^+);

N-{1-[8-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-isopropyl-*N*-methylbenzenesulfonamide; MS (ESI) 526 (MH^+); and

biphenyl-4-sulfonic acid {1-[8-chloro-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 560 (MH^+).

U. In a similar manner as described above in Paragraph A, 3-(4-methoxyphenyl)-7-methyl-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one, as prepared above in Example 5, was condensed with 4-*tert*-butylbenzenesulfonyl chloride to yield 4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 520 (MH^+).

V. In a similar manner as described above in Paragraph U, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-isopropyl-*N*-{1-[3-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 506 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 540 (MH^+);

N-{1-[3-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 478 (MH^+);

4-methoxy-*N*-{1-[3-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 494 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 472 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 484 (MH^+);

4-butyl-*N*-{1-[3-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 520 (MH^+);

N-{1-[3-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-4-trifluoromethylbenzenesulfonamide; MS (ESI) 532 (MH^+); and

2,4,6-trichloro-*N*-{1-[3-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 566 (MH^+).

W. In a similar manner as described above in Paragraph A, 8-

methoxy-3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one, as prepared above in Example 5, was condensed with 4-*tert*-butylbenzenesulfonyl chloride to yield 4-*tert*-butyl-*N*-{1-[8-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 536 (MH^+).

X. In a similar manner as described above in Paragraph W, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-isopropyl-*N*-{1-[8-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 522 (MH^+);

biphenyl-4-sulfonic acid {1-[8-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 556 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[8-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 488 (MH^+); and

4-*tert*-butyl-*N*-{1-[8-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 500 (MH^+).

Y. In a similar manner as described above in Paragraph A, 5-methoxy-3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one, as prepared above in Example 5, was condensed with 4-*tert*-butylbenzenesulfonyl chloride to yield 4-*tert*-butyl-*N*-{1-[5-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 536 (MH^+).

Z. In a similar manner as described above in Paragraph Y, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-isopropyl-*N*-{1-[5-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 522 (MH^+);

biphenyl-4-sulfonic acid {1-[5-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 556 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[5-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 488 (MH^+); and

4-*tert*-butyl-*N*-{1-[5-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 500 (MH^+).

AA. In a similar manner as described above in Paragraph A, but replacing 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one with 6-methoxy-3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one and 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-isopropyl-*N*-{1-[6-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 522 (MH^+);

biphenyl-4-sulfonic acid {1-[6-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 556 (MH^+); and

benzo[1,3]dioxole-5-carboxylic acid {1-[6-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 488 (MH^+).

BB. In a similar manner as described above in Paragraph A, but replacing *p*-anisidine as an intermediate starting material in a prior step with 4-*tert*-butylaniline, the following compound was prepared:

4-*tert*-butyl-*N*-{1-[3-(4-*tert*-butyl-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 532 (MH^+).

CC. In a similar manner as described above in Paragraph BB, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

N-{1-[3-(4-*tert*-butyl-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-isopropyl-*N*-methylbenzenesulfonamide; MS (ESI) 518 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(4-*tert*-butyl-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 552 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4-*tert*-butyl-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 496 (MH^+); and

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(4-*tert*-butyl-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 484 (MH^+).

DD. In a similar manner as described above in Paragraph A, but replacing *p*-anisidine as an intermediate starting material in a prior step with *m*-anisidine, the following compound was prepared:

4-*tert*-butyl-*N*-{1-[3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-

yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 506 (MH^+).

EE. In a similar manner as described above in Paragraph DD, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-isopropyl-*N*-{1-[3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 492 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 526 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 470 (MH^+); and

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 458 (MH^+).

FF. In a similar manner as described above in Paragraph A, but replacing *p*-anisidine as an intermediate starting material in a prior step with *o*-anisidine, the following compound was prepared:

4-*tert*-butyl-*N*-{1-[3-(2-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 506 (MH^+).

GG. In a similar manner as described above in Paragraph FF, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-isopropyl-*N*-{1-[3-(2-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 492 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(2-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 526 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(2-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 470 (MH^+); and

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(2-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 458 (MH^+).

HH. In a similar manner as described above in Paragraph A, but replacing *p*-anisidine as an intermediate starting material in a prior step with 4-trifluoromethoxyaniline, the following compound was prepared:

4-*tert*-butyl-*N*-methyl-*N*-{1-[4-oxo-3-(4-trifluoromethoxyphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}-benzenesulfonamide; MS (ESI) 560 (MH^+).

II. In a similar manner as described above in Paragraph HH, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-isopropyl-*N*-methyl-*N*-{1-[4-oxo-3-(4-trifluoromethoxyphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}-benzenesulfonamide; MS (ESI) 546 (MH^+);

biphenyl-4-sulfonic acid methyl-{1-[4-oxo-3-(4-trifluoromethoxyphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}-amide; MS (ESI) 580 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-{1-[4-oxo-3-(4-trifluoromethoxyphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}-benzamide; MS (ESI) 524 (MH^+); and

benzo[1,3]dioxole-5-carboxylic acid methyl-{1-[4-oxo-3-(4-trifluoromethoxyphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}-amide; MS (ESI) 512 (MH^+).

JJ. In a similar manner as described above in Paragraph A, but replacing *p*-anisidine as an intermediate starting material in a prior step with 4-trifluoromethylaniline, the following compound was prepared:

4-*tert*-butyl-*N*-methyl-*N*-{1-[4-oxo-3-(4-trifluoromethylphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}-benzenesulfonamide; MS (ESI) 544 (MH^+).

KK. In a similar manner as described above in Paragraph JJ, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-isopropyl-*N*-methyl-*N*-{1-[4-oxo-3-(4-trifluoromethylphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}-benzenesulfonamide; MS (ESI) 530 (MH^+);

biphenyl-4-sulfonic acid methyl-{1-[4-oxo-3-(4-trifluoromethylphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}-amide; MS (ESI) 564 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid methyl-{1-[4-oxo-3-(4-trifluoromethylphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}-amide; MS (ESI) 496 (MH^+); and

4-*tert*-butyl-*N*-methyl-*N*-{1-[4-oxo-3-(4-trifluoromethylphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}-benzamide; MS (ESI) 508 (MH^+).

EXAMPLE 8

PREPARATION OF 4-*TERT*-BUTYL-*N*-{1-[3-(4-METHOXYPHENYL)-4-OXO-3,4-DIHYDROQUINAZOLIN-2-YL]ETHYL}-*N*-METHYLBENZAMIDE AND RELATED COMPOUNDS

A. To a suspension of the 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3H-quinazolin-4-one (50 mg, 0.16 mmol) stirring in 2 mL DCM was added TEA (19 mg, 0.19 mmol) followed by the addition of neat 4-*tert*-butylbenzoyl chloride (31 mg, 0.16 mmol). The reaction was allowed to stir at room temperature for 2 h then treated with tris-amine (100 mg). The reaction was allowed to stand for 15 min at room temperature after which the resin was removed by filtration. The filtrate was concentrated under vacuum to afford the crude product. The crude residue was purified by flash chromatography (silica gel, 50% EtOAc/Hex) to afford the desired product as an off white powder (73 mg, 97 % yield). ^{1}H-NMR ($CDCl_3$): δ 8.15 (d, 1H), 7.55 (m, 1H), 7.39 (m, 4H), 7.25 (d, 1H), 7.16 (m, 2H), 7.09 (m, 1H), 6.70 (m, 2H), 4.90 (q, 1H), 4.83 (s, 3H), 3.11 (s, 3H) 1.22 (d, 3H), 1.09 (s, 9H); MS (ESI) 470 (MH^+) .

B. In a similar manner, but replacing 4-*tert*-butylbenzoyl chloride with octanoyl chloride and 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one with 3-(2,4-dimethylphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one, the following compound was made:

nonanoic acid {1-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; ^{1}H-NMR ($CDCl_3$): δ 8.32 (m, 1H), 7.80 (m, 2H), 7.55 (m, 1H), 7.19 (m, 2H), 7.06 (m, 1H), 5.44 (q, 1H), 2.92 (m, 3H), 2.39 (m, 3H), 2.25 (m, 2H), 2.03 (m, 3H), 1.47 (m, 5H), 1.29 (m, 10H), 0.9 (m, 3H); MS (ESI) 448 (MH^+).

C. In a similar as described above in Paragraph A, but replacing 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one with the appropriate starting material, the following compounds were made:

4-*tert*-butyl-*N*-{1-[3-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; ^{1}H-NMR ($CDCl_3$): δ 8.31 (d, 1H), 7.80 (t, 1H), 7.73 (m, 1H), 7.64 (m, 1H), 7.52 (t, 1H), 7.42 (m, 2H), 7.29 (m, 5H), 5.8 (q, 1H), 3.15 (s, 3H), 1.53 (d, 3H), 1.34 (s, 9H); MS (ESI) 458 (MH^+);

4-*tert*-butyl-*N*-{1-[6-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-

dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; ^{1}H-NMR ($CDCl_3$): δ 7.63 (m, 2H), 7.48 (m, 1H), 7.37 (m, 3H), 7.28 (m, 2H), 7.21 (m, 1H), 7.04 (m, 2H), 5.46 (q, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 1.48 (d, 3H), 1.31 (s, 9H); MS (ESI) 500 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-6-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; ^{1}H-NMR ($CDCl_3$): δ 8.06 (m, 1H), 7.59 (m, 2H), 7.49 (m, 1H), 7.38 (m, 2H), 7.28 (m, 2H), 7.21 (m, 1H), 7.04 (m, 2H), 5.45 (q, 1H), 3.83 (s, 3H), 3.08 (s, 3H), 2.49 (s, 3H), 1.48 (d, 3H), 1.31 (s, 9H); MS (ESI) 484 (MH^+); and

4-*tert*-butyl-*N*-methyl-*N*-[1-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl]benzamide; ^{1}H-NMR ($CDCl_3$): δ 8.65 (d, 1H), 7.59 (broad, 1H), 7.44 (m, 5H), 7.08 (t, 1H), 6.22 (q, 1H), 3.02 (s, 3H), 3.01 (s, 3H), 1.54 (d, 3H), 1.33 (s, 9H); MS (ESI) 378 (MH^+).

D. In a similar manner as described above in Paragraph A, but replacing 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one with 3-(4-fluorophenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one and 4-*tert*-butylbenzoyl choride with the appropriate starting material, the following compounds were made:

4-*tert*-butyl-*N*-{1-[3-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 494 (MH^+);

N-{1-[3-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-isopropyl-*N*-methylbenzenesulfonamide; MS (ESI) 480 (MH^+); and

biphenyl-4-sulfonic acid {1-[3-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 514 (MH^+).

E. In a similar manner, but replacing 3-(4-methoxyphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one with 3-(4-methoxyphenyl)-6-methyl-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one and replacing 4-*tert*-butylbenzoyl chloride with the appropriate starting material, the following compounds were made:

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-6-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 520 (MH^+);

4-isopropyl-*N*-{1-[3-(4-methoxyphenyl)-6-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 506 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(4-methoxyphenyl)-6-methyl-4-oxo-3,4-

dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 540 (MH^+);

N-{1-[3-(4-methoxyphenyl)-6-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 478 (MH^+);

4-methoxy-*N*-{1-[3-(4-methoxyphenyl)-6-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 494 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(4-methoxyphenyl)-6-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 472 (MH^+);

4-butyl-*N*-{1-[3-(4-methoxyphenyl)-6-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 520 (MH^+);

N-{1-[3-(4-methoxyphenyl)-6-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-4-trifluoromethylbenzenesulfonamide; MS (ESI) 532 (MH^+); and

2,4,6-trichloro-*N*-{1-[3-(4-methoxyphenyl)-6-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 566 (MH^+).

EXAMPLE 9

PREPARATION OF *N*-[1-(3-BIPHENYL-4-YL-4-OXO-3,4-DIHYDROQUINAZOLIN-2-YL)ETHYL]-4-*TERT*-BUTYL-*N*-METHYLBENZENESULFONAMIDE AND RELATED COMPOUNDS

A. An oven-dried flask charged with *N*-{1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-*tert*-butyl-*N*-methylbenzenesulfonamide (103 mg, 0.19 mmol) was diluted with 2 mL of a nitrogen-purged solution of DME/H_2O (1:1). The resulting reaction mixture was then treated with K_2CO_3 (78.8 mg, 0.57 mmol) and phenyl boronic acid (46.3 mg, 0.38 mmol) at room temperature under a nitrogen atmosphere. In a separate oven dried vial containing triphenyl phosphine (43.9 mg, 0.17 mmol) and Pd_2dba_3:$CHCl_3$ (17 mg, 0.019 mmol) was placed 1 mL of the nitrogen purged DME/H_2O solution (1:1). The contents of the vial were stirred until the Pd(0) was completely dissolved. The premixed palladium solution was then added to the reaction mixture and heated to 70°C under nitrogen for 16 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The resulting residue was then taken up in EtOAc and filtered through a plug of silica. The filtrate was

concentrated under vacuum to afford a crude residue that was purified by chromatography (silica gel, 0-75% EtOAC:Hex) to afford the desired product as a white solid (74 mg, 71% yield). ^{1}H-NMR ($CDCl_3$): δ 8.26 (d, 1H), 7.88 (d, 1H), 7.76 (d, 1H), 7.67 (m, 4H), 7.45 (m, 7H), 7.23 (m, 3H), 4.99 (q, 1H), 3.20 (s, 3H), 1.33 (d, 3H), 1.16 (s, 9H); MS (ESI) 552 (MH^+).

B. In a similar manner, but replacing phenyl boronic acid with the appropriate starting material, the following compounds were made:

4-*tert*-butyl-*N*-methyl-*N*-{1-[4-oxo-3-(4-thiophen-2-ylphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}benzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.23 (m, 1H), 7.79 (m, 1H), 7.67 (m, 3H), 7.47 (m, 7H), 7.39 (m, 2H), 7.08 (m, 1H), 4.90 (q, 1H), 3.12 (s, 3H), 3.12 (s, 3H), 1.29 (d, 3H), 1.20 (s, 9H); MS (ESI) 558 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(3'-methoxy-biphenyl-4-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.25 (d, 1H), 7.87 (m, 1H), 7.75 (m, 1H), 7.65 (m, 2h), 7.52 (m, 2H), 7.41 (m, 3H), 7.25 (m, 5H), 6.95 (m, 1H), 4.98 (q, 1H), 3.89 (s, 3H), 3.20 (s, 3H), 1.31 (d, 3H), 1.16 (s, 9H); MS (ESI) 582 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(3'-chloro-biphenyl-4-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.25 (d, 1H), 7.86 (m, 1H), 7.73 (m, 1H), 7.66 (m, 3H), 7.55 (m, 1H), 7.52 (d, 2H), 7.46 (t, 1H), 7.40 (m, 3H), 7.26 (m, 3H), 4.97 (q, 1H), 3.16 (d, 3H), 1.31 (d, 3H), 1.17 (s, 9H); MS (ESI) 587 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-{1-[3-(2'-methyl-biphenyl-4-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-benzenesulfonamide; MS (ESI) 566 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-{1-[3-(3'-methyl-biphenyl-4-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-benzenesulfonamide; MS (ESI) 566 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-{1-[3-(4'-methyl-biphenyl-4-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-benzenesulfonamide; MS (ESI) 566 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(2'-chloro-biphenyl-4-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 586 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4'-chloro-biphenyl-4-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 586 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(2'-methoxy-biphenyl-4-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 582 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4'-methoxy-biphenyl-4-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 582 (MH^+);

4'-(2-{1-[(4-*tert*-butylbenzenesulfonyl)methylamino]ethyl}-4-oxo-4*H*-quinazolin-3-yl)-biphenyl-4-carboxylic acid; MS (ESI) 596 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4'-cyano-biphenyl-4-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 577 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-{1-[4-oxo-3-(4-thiophen-3-ylphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}benzenesulfonamide; MS (ESI) 558 (MH^+);

4'-(2-{1-[(4-*tert*-butylbenzenesulfonyl)methylamino]ethyl}-4-oxo-4*H*-quinazolin-3-yl)-biphenyl-3-carboxylic acid methyl ester; MS (ESI) 610 (MH^+);

4'-(2-{1-[(4-*tert*-butylbenzenesulfonyl)methylamino]ethyl}-4-oxo-4*H*-quinazolin-3-yl)-biphenyl-4-carboxylic acid methyl ester; MS (ESI) 610 (MH^+);

4'-(2-{1-[(4-*tert*-butylbenzenesulfonyl)-methylamino]ethyl}-4-oxo-4*H*-quinazolin-3-yl)-biphenyl-3-carboxylic acid; MS (ESI) 596 (MH^+); and

C. The following three compounds were made by a modification of the procedure in paragraph B, as described in Wolfe *et al., J. Org. Chem.* (2000), Vol. 65, pp. 1158-1174.

4-*tert*-butyl-*N*-methyl-*N*-{1-[4-oxo-3-(4-piperidin-1-yl-phenyl)-3,4-dihydroquinazolin-2-yl]ethyl}benzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.21 (m, 1H), 7.60 (m, 2H), 7.51 (d, 2H), 7.39 (m, 2H), 7.20 (m, 2H), 7.13 (m, 1H), 7.00 (m, 2H), 5.01 (q, 1H), 3.29 (m, 4H), 3.23 (s, 3H), 1.74 (m, 4H), 1.30 (d, 3H), 1.26 (m, 2H), 1.14 (s, 9H);MS (ESI) 559 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-{1-[4-oxo-3-(4-pyrrolidin-1-ylphenyl)-3,4-dihydroquinazolin-2-yl]ethyl}benzenesulfonamide; MS (ESI) 545 (MH^+); and

4-*tert*-butyl-*N*-methyl-*N*-{1-[3-(4-morpholin-4-ylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}benzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.22 (d, 1H), 7.62 (m, 1H), 7.52 (d, 2H), 7.424 (m, 2H), 7.30 (d, 1H), t.22 (d, 2H), 7.14 (d, 1H), 7.03 (m, 2H), 5.01 (q, 1H), 3.90 (s, 3H), 3.28 (m, 3H), 3.21 (s, 3H), 1.31 (d, 3H), 1.14 (s, 9H); MS (ESI) 561 (MH^+).

D. In a similar manner as described above in Paragraph A, but replacing phenyl boronic acid with thiophene-2-boronic acid and *N*-{1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-*tert*-butyl-*N*-methylbenzenesulfonamide with *N*-[1-(6-bromo-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-4-*tert*-butyl-*N*-methylbenzenesulfonamide, the following compound was made:

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-6-thiophen-2-yl-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.34 (d, 1H), 7.71 (m, 2H), 7.5 (d, 2H), 7.46 (m, 3H), 7.35 (d, 1H), 7.22 (m, 4H) 7.05 (d, 1H), 4.92 (q, 1H), 3.17 (s, 3H), 2.48 (s, 3H), 1.29 (d, 3H), 1.19 (s, 9H); MS (ESI) 570 (MH^+).

E. In a similar manner as described above in Paragraph D, but replacing thiophene-2-boronic acid with the appropriate starting material, the following compounds were made:

4-[2-{1-[(4-*tert*-butyl-benzenesulfonyl)methylamino]ethyl}-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]benzoic acid; ^{1}H-NMR ($CDCl_3$): δ 8.48 (d, 1H), 8.21 (m, 2H), 7.92 (m, 1H), 7.74 (d, 2H), 7.54 (d, 2H), 7.46 (m, 4H), 7.36 (m, 1H), 7.24 (m, 1H), 7.08 (m, 1H), 4.96 (q, 1H), 3.21 (s, 3H), 2.49 (s, 3H), 1.32 (d, 3H), 1.15 (s, 9H); MS (ESI) 610 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-6-m-tolyl-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.41 (m, 1H), 7.87 (m, 2H), 7.53 (m, 2H), 7.45 (m, 3H), 7.37 (m, 3H), 7.23 (m, 3H), 7.07 (m, 1H), 4.96 (q, 1H), 3.21 (s, 3H), 2.49 (s, 3H), 2.43 (s, 3H), 1.32 (d, 3H), 1.15 (s, 9H); MS (ESI) 580 (MH^+);

4-*tert*-butyl-*N*-{1-[6-(3-chlorophenyl)-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.39 (d, 1H), 7.84 (m, 1H), 7.61 (m, 1H), 7.53 (m, 2H), 7.47 (m, 3H), 7.40 (d, 2H), 7.37 (m, 2H), 7.24 (m, 2H), 7.07 (m, 1H), 4.95 (q, 1H), 3.20 (s, 3H), 2.49 (s, 3H), 1.31 (d, 3H), 1.15 (s, 9H); MS (ESI) 601 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-6-thiophen-3-yl-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.33 (d, 1H), 7.71 (m, 1H), 7.50 (m, 3H), 7.44 (m, 3H), 7.35 (m, 1H), 7.22 (m, 4H), 7.04 (m,

1H), 4.91 (q, 1H), 3.17 (s, 3H), 2.48 (s, 3H), 1.29 (d, 3H), 1.17 (s, 9H); MS (ESI) 570 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-[1-(4-oxo-6-phenyl-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 566 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-[1-(4-oxo-6-o-tolyl-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 580 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-[1-(4-oxo-3,6-di-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 580 (MH^+);

4-*tert*-butyl-*N*-{1-[6-(2-chlorophenyl)-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 600 (MH^+);

4-*tert*-butyl-*N*-{1-[6-(4-chlorophenyl)-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 600 (MH^+);

4-*tert*-butyl-*N*-{1-[6-(2-methoxyphenyl)-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 596 (MH^+);

4-*tert*-butyl-*N*-{1-[6-(3-methoxyphenyl)-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 596 (MH^+);

4-*tert*-butyl-*N*-{1-[6-(4-methoxyphenyl)-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 596 (MH^+);

3-(2-{1-[(4-*tert*-butyl-benzenesulfonyl)methylamino]ethyl}-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-6-yl)benzoic acid methyl ester; MS (ESI) 624 (MH^+);

4-(2-{1-[(4-*tert*-butyl-benzenesulfonyl)methylamino]ethyl}-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-6-yl)-benzoic acid methyl ester; MS (ESI) 624 (MH^+);

3-(2-{1-[(4-*tert*-butylbenzenesulfonyl)methylamino]ethyl}-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-6-yl)benzoic acid; MS (ESI) 610 (MH^+); and

4-*tert*-butyl-*N*-{1-[6-(4-cyanophenyl)-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 591 (MH^+).

F. The following three compounds were made by a modification of the procedure in paragraph D, as described in Wolfe *et al., J. Org. Chem.* (2000), Vol. 65, pp. 1158-1174.

4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-6-pyrrolidin-1-yl-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 7.51

(d, 2H), 7.43 (m, 2H), 7.33 (d, 1H), 7.24 (m, 3H), 7.17 (m, 1H), 7.05 (d, 1H), 6.93 (d, 1H), 4.92 (q, 1H), 3.35 (m, 4H), 3.12 (s, 3H), 2.47 (s, 3H), 2.04(m, 4H), 1.28 (d, 3H), 1.18 (s, 9H); MS (ESI) 559 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-[1-(6-morpholin-4-yl-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 575 (MH^+); and

4-*tert*-butyl-*N*-methyl-*N*-[1-(4-oxo-6-piperidin-1-yl-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 573 (MH^+).

EXAMPLE 10

PREPARATION OF 4-*TERT*-BUTYL-*N*-{1-[3-(4-HYDROXYPHENYL)-4-OXO-3,4-DIHYDROQUINAZOLIN-2-YL]ETHYL}-*N*-METHYLBENZENESULFONAMIDE AND RELATED COMPOUNDS

A. To a suspension of the 4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide (0.5 g, 1.07 mmol) stirring in 15 mL DCM was added boron tribromide (5 mL, 5 mmol 1M in DCM). The reaction was allowed to stir at room temperature for 15 min after which TLC analysis indicated that starting material was completely consumed. The reaction was quenched with 20 mL brine and the resulting mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer extracted with $CHCl_3$ (2 x 25 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under vacuum to afford a crude residue that was purified by chromatography (silica gel, 0-75% EtOAc:Hex), yielding the desired product as a white solid (0.735 g, 95 %). ^{1}H-NMR ($CDCl_3$): δ 8.26 (d, 1H), 7.67 (t, 1H), 7.51 (d, 2H), 7.45 (t, 1H), 7.36 (m, 2H), 7.26 (d, 2H), 6.98 (m, 1H), 6.90 (m, 2H), 5.00 (q, 1H), 3.19 (s, 3H), 1.28 (d, 3H), 1.17 (s, 9H); MS (ESI) 492 (MH^+).

B. In a similar manner, but replacing 4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide with 4-*tert*-butyl-*N*-[1-(6-methoxy-4-oxo-3-p-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-*N*-methylbenzenesulfonamide, the following compound was made:

4-*tert*-butyl-*N*-[1-(6-hydroxy-4-oxo-3-p-tolyl-3,4-dihydroquinazolin-2-

yl)ethyl]-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 7.82 (d, 1H), 7.49 (m, 3H), 7.42 (d, 1H), 7.36 (d, 1H), 7.24 (m, 4H), 7.06 (d, 1H), 6.21 (s, 1H), 4.94 (q, 1H), 3.13 (s, 3H), 2.48 (s, 3H), 1.27 (d, 3H), 1.18 (s, 9H); MS (ESI) 506 (MH^+).

C. In a similar manner described above in Paragraph A, 4-*tert*-butyl-*N*-{1-[5-hydroxy-3-(4-hydroxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 508 (MH^+); was prepared from 4-*tert*-butyl-*N*-{1-[5-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide, which was prepared as described above in Example 7.

EXAMPLE 11

PREPARATION OF *N*-{1-[3-(4-BENZYLOXYPHENYL)-4-OXO-3,4-DIHYDROQUINAZOLIN-2-YL]ETHYL}-4-*TERT*-BUTYL-*N*-METHYLBENZENESULFONAMIDE AND RELATED COMPOUNDS

A. To a solution of 4-*tert*-butyl-*N*-{1-[3-(4-hydroxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide (50 mg, 0.11 mmol) in anhydrous THF (2 mL) were added triphenylphosphine (0.115 mg, 0.44 mmol), diisopropyl azodicarboxylate (88.9 mg, 0.44 mmol), and benzyl alcohol (48.5 mg, 0.44 mmol) at 0°C. The mixture was stirred for 1 h at this temperature and then allowed to warm to room temperature and stirred overnight. The solvent was evaporated under reduced pressure, and the crude residue was purified by chromatography (silica gel, 0-50% EtOAc:Hex) to yield the desired product as a white solid (48 mg, 80 %). ^{1}H-NMR ($CDCl_3$): δ 8.22 (d, 1H), 7.64 (m, 1H), 7.49 (m, 5H), 7.42 (m, 3H), 7.34 (m, 2H), 7.24 (m, 3H), 7.10 (m, 2H), 5.15 (s, 2H), 4.99 (q, 1H), 3.19 (s, 3H), 1.30 (d, 3H), 1.16 (s, 9H); MS (ESI) 582 (MH^+).

B. In a similar manner, but replacing benzyl alcohol with the appropriate starting material, the following compounds were made:

4-*tert*-butyl-*N*-{1-[3-(4-ethoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.22 (d, 1H), 7.64 (t, 1H), 7.43 (m, 2H), 7.33 (d, 1H), 7.23 (m, 2H), 7.15 (d, 1H), 7.05 (dd, 2H), 4.98 (q, 1H), 4.13 (q, 2H), 3.19 (s, 3H), 1.47 (t, 3H), 1.29 (d, 3H), 1.16 (s, 9H); MS (ESI) 520 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-(1-{4-oxo-3-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-3,4-dihydroquinazolin-2-yl}ethyl)benzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.23 (d, 1H), 7.67 (m, 2H), 7.46 (m, 4H), 7.30 (d, 2H), 7.15 (m, 2H), 7.06 (m, 1H), 5.00 (q, 1H), 4.50 (m, 2H), 3.76 (m, 2H), 3.54 (m, 2H), 3.07 (s, 3H), 1.28 (d, 3H), 1.17 (s, 9H); MS (ESI) 603 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-(1-{3-[4-(2-morpholin-4-yl-ethoxy)phenyl]-4-oxo-3,4-dihydroquinazolin-2-yl}ethyl)benzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.25 (d, 1H), 7.69 (t, 1H), 7.53 (d, 2H), 7.46 (m, 3H), 7.31 (d, 2H), 7.15 (m, 2H), 7.07 (m, 1H), 5.00 (q, 1H), 4.52 (m, 2H), 4.01 (m, 4H) 3.71 (m, 2H), 3.58 (m, 2H), 3.09 (m, 2H), 3.03 (m, 2H), 2.72 (s, 3H), 1.28 (d, 3H), 1.21 (s, 9H); MS (ESI) 605 (MH^+);

[4-(2-{1-[(4-*tert*-butylbenzenesulfonyl)methylamino]ethyl}-4-oxo-4*H*-quinazolin-3-yl)phenoxy]acetic acid ethyl ester; ^{1}H-NMR ($CDCl_3$): δ 8.22 (d, 1H, 7.65 (t, 1H), 7.50 (d, 3H), 7.44 (t, 1H), 7.36 (d, 1H), 7.27 (s, 2H), 7.16 (d, 1H), 7.10 (s, 2H), 4.94 (q, 1H), 4.71 (s, 2H), 4.31 (q, 2H), 3.17 (s, 3H), 1.33 (t, 3H), 1.26 (d, 2H), 1.18 (s, 9H); MS (ESI) 578 (MH^+);

4-*tert*-butyl-*N*-(1-{3-[4-(2-methoxyethoxy)phenyl]-4-oxo-3,4-dihydroquinazolin-2-yl}ethyl)-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 8.22 (d, 1H), 7.64 (t, 1H), 7.45 (m, 4H), 7.33 (d, 1h), 7.21 (m, 3H), 7.09 (s, 2H), 4.97 (q, 1H), 4.22 (t, 2H), 3.81 (t, 2H), 3.49 (s, 3H), 3.19 (d, 3H), 1.28 (d, 3H), 1.17 (s, 9H); MS (ESI) 550 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4-*n*-butoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide;

4-*tert*-butyl-*N*-{1-[3-(4-isopropoxy-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 534 (MH^+); and

4-*tert*-butyl-*N*-{1-[3-(4-isobutoxy-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 548 (MH^+).

C. In a similar manner as described above in Paragraph A, but replacing 4-*tert*-butyl-*N*-{1-[3-(4-hydroxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide with 4-*tert*-butyl-*N*-[1-(6-hydroxy-4-oxo-3-p-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-*N*-methylbenzenesulfonamide, the following compounds was made:

N-[1-(6-benzyloxy-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-4-*tert*-butyl-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 7.67 (d, 1H), 7.50 (m, 2H), 7.44 (m, 4H), 7.39 (m, 2H), 7.34 (m, 2H), 7.30 (m, 2H), 7.24 (m, 1H), 7.05 (m, 1H), 5.13 (s, 2H), 4.93 (q, 1H), 3.14 (s, 3H), 2.48 (s, 3H), 1.28 (d, 3H), 1.18 (s, 9H); MS (ESI) 596 (MH^+).

D. In a similar manner as described above in Paragraph C, but replacing benzyl alcohol with the appropriate starting material, the following compounds were made:

4-*tert*-butyl-*N*-[1-(6-isobutoxy-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 7.54 (d, 1H), 7.50 (m, 2H), 7.45 (m, 1H), 7.43 (m, 1H), 7.33 (m, 1H), 7.24 (m, 4H), 7.04 (m, 1H), 4.93 (q, 1H), 3.79 (d, 2H), 3.15 (s, 3H), 2.48 (s, 3H), 1.28 (d, 3H), 1.17 (s, 9H); MS (ESI) 562 (MH^+);

N-[1-(6-butoxy-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-4-*tert*-butyl-*N*-methylbenzenesulfonamide; ^{1}H-NMR ($CDCl_3$): δ 7.5 (m, 3H), 7.46 (m, 1H), 7.40 (m, 1H), 7.34 (m, 3H), 7.26 (m, 2H), 7.05 (m, 1H), 4.94 (q, 1H), 4.69 (s, 2H), 4.27 (q, 2H), 3.13 (s, 3H), 2.48 (s, 3H), 1.31 (t, 3H), 1.27 (d, 3H), 1.19 (s, 9H); MS (ESI) 562 (MH^+);

(2-{1-[(4-*tert*-butylbenzenesulfonyl)methylamino]ethyl}-4-oxo-3-p-tolyl-3,4-dihydroquinazolin-6-yloxy)acetic acid ethyl ester; ^{1}H-NMR ($CDCl_3$): δ 7.56 (d, 1H), 7.50 (m, 2H), 7.44 (m, 2H), 7.33 (m, 1H), 7.24 (m, 4H), 7.05 (m, 1H), 4.93 (q, 1H), 4.03 (t, 2H), 3.15 (s, 3H), 2.48 (s, 3H), 1.79 (m, 2H), 1.5 (m, 2H), 1.28 (d, 1H), 1.18 (s, 9H), 0.98 (t, 3H); MS (ESI) 592 (MH^+);

4-*tert*-butyl-*N*-[1-(6-ethoxy-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-*N*-methylbenzenesulfonamide; MS (ESI) 534 (MH^+); and

4-*tert*-butyl-*N*-[1-(6-isopropoxy-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethyl]-*N*-methylbenzenesulfonamide; MS (ESI) 548 (MH^+).

E. In a similar manner as described in Paragraph A, but replacing the intermediate starting material, 4-*tert*-butylbenzenesulfonyl chloride, in a prior step, with an appropriate intermediate starting material, the following compounds were made:

N-{1-[3-(4-benzyloxy-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-

isopropyl-*N*-methylbenzenesulfonamide; MS (ESI) 568 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(4-benzyloxy-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 602 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(4-benzyloxy-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 534 (MH^+); and

N-{1-[3-(4-benzyloxy-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-*tert*-butyl-*N*-methylbenzamide; MS (ESI) 546 (MH^+).

EXAMPLE 12

PREPARATION OF 3-(4-BROMOPHENYL)-2-(1-METHYLAMINOETHYL)-3*H*-QUINAZOLIN-4-ONE AND RELATED COMPOUNDS

A. The title compound was prepared from 3-(4-bromophenyl)-2-(1-chloroethyl)-3*H*-quinazolin-4-one (as prepared above in Example 3) and methylamine under conditions similar to those described in Example 5 above, MS (ESI) 358 (MH^+).

B. In a similar manner as described above in Example 7, 3-(4-bromophenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one was condensed with benzylsulfonyl chloride to yield *N*-{1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 498 (MH^+).

C. In a similar manner as described above in Paragraph B, but replacing benzylsulfonyl chloride with the appropriate starting material, the following compounds were prepared:

N-{1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-methoxy-*N*-methylbenzenesulfonamide; MS (ESI) 528 (MH^+);

N-{1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 512 (MH^+);

N-{1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-chloro-*N*-methylbenzenesulfonamide; MS (ESI) 533 (MH^+);

N-{1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-*tert*-butyl-*N*-methylbenzenesulfonamide; MS (ESI) 554 (MH^+);

N-{1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-

isopropyl-*N*-methylbenzenesulfonamide; MS (ESI) 540 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 574 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 506 (MH^+);

N-{1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-4-trifluoromethylbenzenesulfonamide; MS (ESI) 566 (MH^+); and

N-{1-[3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-*tert*-butyl-*N*-methylbenzamide; MS (ESI) 518 (MH^+).

EXAMPLE 13

PREPARATION OF 2-(1-METHYLAMINOETHYL)-3-PHENYL-3*H*-QUINAZOLIN-4-ONE AND RELATED COMPOUNDS

A. In a similar manner as described above in Example 3 and Example 5, but replacing *p*-anisidine with aniline, the title compound was prepared; MS (ESI) 280 (MH^+).

B. In a similar manner as described above, but replacing *p*-anisidine with 4-fluoroaniline, the following compound was prepared:

3-(4-fluorophenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one; MS (ESI) 298 (MH^+).

C. In a similar manner as described above in Example 7, 2-(1-methylaminoethyl)-3-phenyl-3*H*-quinazolin-4-one, prepared as described above in Paragraph A, was condensed with benzenesulfonyl chloride to yield *N*-methyl-*N*-[1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 420 (MH^+).

D. In a similar manner as described above, but replacing benzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-methoxy-*N*-methyl-*N*-[1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 450 (MH^+);

4,*N*-dimethyl-*N*-[1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 434 (MH^+);

4-chloro-*N*-methyl-*N*-[1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 454 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-[1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 476 (MH^+);

4-isopropyl-*N*-methyl-*N*-[1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl]benzenesulfonamide; MS (ESI) 462 (MH^+);

biphenyl-4-sulfonic acid methyl-[1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl]amide; MS (ESI) 496 (MH^+);

4-*tert*-butyl-*N*-methyl-*N*-[1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl]benzamide; MS (ESI) 440 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid methyl-[1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl]amide; MS (ESI) 428 (MH^+); and

N-methyl-*N*-[1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl]-4-trifluoromethylbenzenesulfonamide; MS (ESI) 488 (MH^+).

E. In a similar manner as described above in Paragraph A, but replacing but replacing *p*-anisidine with 4-chloroaniline, the following compound was prepared:

3-(4-chlorophenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one; MS (ESI) 314 (MH^+).

F. In a similar manner as described above in Example 7, 3-(4-chlorophenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one was condensed with *o*-anisoyl chloride to yield *N*-{1-[3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-2-methoxy-*N*-methylbenzamide; MS (ESI) 448 (MH^+).

G. In a similar manner as described above in Paragraph F, but replacing *o*-anisoyl chloride with the appropriate starting material, the following compounds were made:

N-{1-[3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-3-methoxy-*N*-methylbenzamide; MS (ESI) 448 (MH^+);

N-{1-[3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-

methoxy-*N*-methylbenzamide; MS (ESI) 448 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 462 (MH^+);

N-{1-[3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-terephthalamic acid methyl ester; MS (ESI) 476 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 474 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 510 (MH^+);

N-{1-[3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-methoxy-*N*-methylbenzenesulfonamide; MS (ESI) 484 (MH^+); and

nonanoic acid {1-[3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 454 (MH^+).

H. In a similar manner as described above in Example 3, Example 5 and Example 7, but replacing *p*-anisidine with 4-aminobenzonitrile, the following compound was prepared:

4-*tert*-butyl-*N*-{1-[3-(4-cyanophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 501 (MH^+).

I. 4-*tert*-Butyl-*N*-{1-[3-(4-cyanophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide, prepared as described above in Paragraph H, was hydrolyzed with concentrated HCl at reflux to yield 4-(2-{1-[(4-*tert*-butyl-benzenesulfonyl)methylamino]ethyl}-4-oxo-4*H*-quinazolin-3-yl)-benzoic acid; MS (ESI) 520 (MH^+).

J. In a similar manner as described above in Example 3 and Example 5, but replacing *p*-anisidine with 3,5-dimethylaniline, the following compound was made:

3-(3,5-dimethylphenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one; MS (ESI) 308 (MH^+).

K. In a similar manner as described above in Paragraph J, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

4-*tert*-butyl-*N*-{1-[3-(3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 468 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 456 (MH^+);

4-*tert*-butyl-*N*-{1-[3-(3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 504 (MH^+);

N-{1-[3-(3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-isopropyl-*N*-methylbenzenesulfonamide; MS (ESI) 490 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 524 (MH^+);

N-{1-[3-(3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 462 (MH^+);

N-{1-[3-(3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-methoxy-*N*-methylbenzenesulfonamide; MS (ESI) 478 (MH^+);

N-{1-[3-(3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 448 (MH^+);

4-chloro-*N*-{1-[3-(3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 482 (MH^+); and

N-{1-[3-(3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methyl-4-trifluoromethylbenzenesulfonamide; MS (ESI) 516 (MH^+).

L. In a similar manner as described above in Example 3 and Example 5, but replacing *p*-anisidine with 4-dimethylaminoaniline, the following compound was made:

3-(4-dimethylamino-phenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one; MS (ESI) 323 (MH^+).

M. In a similar manner as described above in Example 7, 3-(4-dimethylamino-phenyl)-2-(1-methylaminoethyl)-3*H*-quinazolin-4-one, as prepared above in Paragraph L, was condensed with 4-*tert*-butylbenzenesulfonyl chloride to yield 4-*tert*-butyl-*N*-{1-[3-(4-dimethylamino-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide; MS (ESI) 519 (MH^+).

N. In a similar manner as described above in Paragraph M, but

replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

N-{1-[3-(4-dimethylamino-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-4-isopropyl-*N*-methylbenzenesulfonamide; MS (ESI) 505 (MH^+);

biphenyl-4-sulfonic acid {1-[3-(4-dimethylamino-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 539 (MH^+);

benzo[1,3]dioxole-5-carboxylic acid {1-[3-(4-dimethylamino-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}methylamide; MS (ESI) 471 (MH^+); and

4-*tert*-butyl-*N*-{1-[3-(4-dimethylamino-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzamide; MS (ESI) 483 (MH^+).

EXAMPLE 14

PREPARATION OF 4-*TERT*-BUTYL-*N*-[3-(2,4-DIMETHYLPHENYL)-4-OXO-3,4-DIHYDROQUINAZOLIN-2-YLMETHYL]-*N*-METHYLBENZENESULFONAMIDE AND RELATED COMPOUNDS

A. In a similar manner as described above in Example 3 and Example 5, but with the appropriate starting materials, the following compound was prepared:

3-(2,4-dimethylphenyl)-2-methylamino-methyl-3*H*-quinazolin-4-one; MS (ESI) 294 (MH^+).

B. In a similar manner as described above in Example 7, 3-(2,4-dimethylphenyl)-2-methylamino-methyl-3*H*-quinazolin-4-one was condensed with 4-*tert*-butylbenzenesulfonyl chloride to yield the title compound, MS (ESI) 490 (MH^+).

C. In a similar manner as described above, but replacing 4-*tert*-butylbenzenesulfonyl chloride with the appropriate starting material, the following compounds were made:

benzo[1,3]dioxole-5-carboxylic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]methylamide; MS (ESI) 442 (MH^+);

4-*tert*-butyl-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methylbenzamide; MS (ESI) 454 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-4-methoxy-*N*-methylbenzenesulfonamide; MS (ESI) 464 (MH^+);

4-chloro-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methylbenzenesulfonamide; MS (ESI) 468 (MH^+);

octane-1-sulfonic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]methylamide; MS (ESI) 470 (MH^+);

quinoline-8-sulfonic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]methylamide; MS (ESI) 485 (MH^+);

naphthalene-1-sulfonic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]methylamide; MS (ESI) 484 (MH^+);

2-naphthalen-1-yl-ethanesulfonic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]methylamide; MS (ESI) 512 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-2,*N*-dimethylbenzenesulfonamide; MS (ESI) 448 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-3,*N*-dimethylbenzenesulfonamide; MS (ESI) 448 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 448 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methyl-C-phenyl-methanesulfonamide; MS (ESI) 448 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methyl-3-trifluoromethylbenzenesulfonamide; MS (ESI) 502 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methyl-4-trifluoromethoxy-benzenesulfonamide; MS (ESI) 518 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-2,5,*N*-trimethylbenzenesulfonamide; MS (ESI) 462 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-3,4-dimethoxy-*N*-methylbenzenesulfonamide; MS (ESI) 494 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-2,4,6,*N*-tetramethylbenzenesulfonamide; MS (ESI) 476 (MH^+);

2-phenyl-ethenesulfonic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-

dihydroquinazolin-2-ylmethyl]methylamide; MS (ESI) 460 (MH^+);

2,2,5,6,8-pentamethyl-chroman-7-sulfonic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]methylamide; MS (ESI) 560 (MH^+);

thiophene-2-sulfonic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]methylamide; MS (ESI) 440 (MH^+);

C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methyl-methanesulfonamide; MS (ESI) 508 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-3,4-difluoro-*N*-methylbenzenesulfonamide; MS (ESI) 470 (MH^+);

3-chloro-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-2,*N*-dimethylbenzenesulfonamide; MS (ESI) 482 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-5-fluoro-2,*N*-dimethylbenzenesulfonamide; MS (ESI) 466 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methyl-4-trifluoromethylbenzenesulfonamide; MS (ESI) 502 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-3-fluoro-*N*-methylbenzenesulfonamide; MS (ESI) 452 (MH^+);

2,4,6-trichloro-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methylbenzenesulfonamide; MS (ESI) 536 (MH^+);

3-chloro-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-4-fluoro-*N*-methylbenzenesulfonamide; MS (ESI) 486 (MH^+);

2-chloro-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methylbenzenesulfonamide; MS (ESI) 468 (MH^+);

5-chloro-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-2-methoxy-*N*-methylbenzenesulfonamide; MS (ESI) 498 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-2,5-dimethoxy-*N*-methylbenzenesulfonamide; MS (ESI) 494 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-2,3,4-trifluoro-*N*-methylbenzenesulfonamide; MS (ESI) 488 (MH^+);

3-chloro-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-

ylmethyl]-*N*-methylbenzenesulfonamide; MS (ESI) 468 (MH^+);

biphenyl-4-sulfonic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]methylamide; MS (ESI) 510 (MH^+);

4-cyano-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methylbenzenesulfonamide; MS (ESI) 459 (MH^+);

4-butyl-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methylbenzenesulfonamide; MS (ESI) 490 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-4-(1,1-dimethyl-propyl)-*N*-methylbenzenesulfonamide; MS (ESI) 504 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-4-isopropyl-*N*-methylbenzenesulfonamide; MS (ESI) 476 (MH^+);

4-butoxy-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methylbenzenesulfonamide; MS (ESI) 506 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-3-methoxy-*N*-methylbenzenesulfonamide; MS (ESI) 464 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-2-methoxy-4,*N*-dimethylbenzenesulfonamide; MS (ESI) 478 (MH^+);

4-chloro-*N*-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-2,5,*N*-trimethylbenzenesulfonamide; MS (ESI) 496 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methylmethanesulfonamide; MS (ESI) 372 (MH^+);

butane-1-sulfonic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]methylamide; MS (ESI) 414 (MH^+);

3-chloropropane-1-sulfonic acid [3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]methylamide; MS (ESI) 434 (MH^+);

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methyl-3,5-bis-trifluoromethylbenzenesulfonamide; MS (ESI) 570 (MH^+); and

N-[3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-methyl-4-nitrobenzenesulfonamide; MS (ESI) 479 (MH^+).

EXAMPLE 15

TIME RESOLVED FLUORESCENCE RESONANCE ENERGY TRANSFER (TR-FRET) ASSAY

The FRET assay was performed by incubating 8 nM of GST-FXR-LBD (comprising glutathione-S-transferase fused in frame to the FXR LBD, (amino acids 244-471 of human FXR), 8 nM of Europium-labeled anti-GST antibody (Wallac/PE Life Sciences Cat#AD0064), 16 nM biotin-SRC-1 peptide [5'-biotin-CPSSHSSLTERHKILHRLLQEGSPS-CONH2], 20 nM APC-SA [allophycocyanin conjugated streptavidin] (Wallac/PE Life Sciences, Cat# AD0059A) in FRET assay buffer (20 mM KH_2PO_4/K_2HPO_4 (pH 7.3), 150 mM NaCl, 2 mM CHAPS, 2 mM EDTA, 1 mM DTT) in the presence of the test compound(s) for 2-4 hours at room temperature. Data was collected using an LJL Analyst with readings at 615 nm and 665 nm after a delay of 65 μs and an excitation wavelength of 330 nm.

EXAMPLE 16

FXR CO-TRANSFECTION ASSAY

The basic co-transfection protocol for measuring FXR activity is as follows. CV-1 African Green Monkey Kidney cells are plated 24 hours before transfection to achieve approximately 70-80 percent confluency. Cells are transfected with CMX-hFXR, CMX-RXRα, Luc12 reporter (ECREx7-Tk-Luciferase), and a CMX-β-Galactosidase expression vector (See WO 00/76523). The transfection reagent used is DOTAP (Boehringer Mannheim). Cells are incubated with the DOTAP/DNA mixture for 5 hours after which the cells are harvested and plated onto either 96 well or 384 well plates containing the appropriate concentration of test compound. The assay is allowed to continue for an additional 18-20 hours, after which the cells are lysed, with lysis buffer (1 % triton X 100, 10 % glycerol, 5 mM Dithiothreitol, 1 mM EGTA, 25 mM Tricine, pH 7.8) and the luciferase activity is measured in the presence of Luciferase assay buffer (0.73 mM ATP, 22.3 mM Tricine, 0.11 mM EGTA, 0.55 mM Luciferin, 0.15 mM Coenzyme A, 0.5 mM HEPES, 10 mM Magnesium sulphate) on a standard

luminomter plate reader (PE Biosystems, NorthStar Reader).

EXAMPLE 17

IN VIVO STUDIES

In order to evaluate direct regulation of key target genes by the compounds of the invention, animals are administered a single oral dose of the test compound and tissues collected at six or fifteen hours after dose. Male C57BL/6 mice (n=8) are dosed by oral gavage with vehicle or compound. At six and fifteen hours after the dose, animals are bled via the retro orbital sinus for plasma collection. Animals are then euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total cholesterol, HDL cholesterol and triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by FXR, knock out mice ($FXR^{-/-}$) and C57BL/6 wild-type controls maybe used in this same protocol.

To compare the effects of compounds on plasma cholesterol and triglycerides, animals are dosed with compound for one week and plasma lipid levels are monitored throughout the study. Male C57BL/6 mice (n=8) are dosed daily by oral gavage with vehicle or compound. Plasma samples are taken on day –1 (in order to group animals), day 1, 3, and 7. Samples are collected three hours after the daily dose. On day 7 of the study, following plasma collection, animals are euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total cholesterol, HDL cholesterol and triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by FXR knockout mice and C57BL/6 wild-type controls maybe used in this same protocol.

Evaluation of compounds to inhibit cholesterol absorption is done via measurement of labeled cholesterol in feces. Male A129 mice (n=7) are dosed daily by oral gavage with vehicle or compound for 7 days. On day 7 of the study, animals

are administered [^{14}C]-cholesterol and [^{3}H]-sitostanol by oral gavage. Animals are individually housed on wire racks for the next 24 hours in order to collect feces. Feces are then dried and ground to a fine powder. Labeled cholesterol and sitostanol are extracted from the feces and ratios of the two are counted on a liquid scintillation counter in order to evaluate the amount of cholesterol absorbed by the individual animal.

RESULTS OF EXAMPLES 15 AND 16

Both the FXR/ECREx7 co-transfection assay (Example 15) and the TR-FRET assay (Example 16) can be used to establish the EC_{50}/IC_{50} values for potency and percent activity or inhibition for efficacy. Efficacy defines the activity of a compound relative to a high control (chenodeoxycholic acid, CDCA) or a low control (DMSO/vehicle). The dose response curves are generated from an 8 point curve with concentrations differing by ½ LOG units. Each point represents the average of 4 wells of data from a 384 well plate. The curve for the data is generated by using the equation:

Y = Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))

The EC_{50}/IC_{50} is therefore defined as the concentration at which an agonist or antagonist elicits a response that is half way between the Top (maximum) and Bottom (baseline) values. The EC_{50}/IC_{50} values represented are the averages of at least 3 independent experiments. The determination of the relative efficacy or % control for an agonist is by comparison to the maximum response achieved by chenodeoxycholic acid that is measured individually in each dose response experiment.

For the antagonist assay, CDCA is added to each well of a 384 well plate to elicit a response. The % inhibition for each antagonist is therefore a measurement of the inhibition of the activity of CDCA. In this example, 100% inhibition would indicate that the activity of CDCA has been reduced to baseline levels, defined as the activity of the assay in the presence of DMSO only.

Most of the compounds disclosed herein and tested exhibited activity in

at least one of the above assays (EC_{50} or IC_{50} less than 10 μM). Most showed activity at below 1 μM. For example, 4-*tert*-butyl-*N*-{1-[3-(4-methoxyphenyl)-4-oxo-6-thiophen-2-yl-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide (Example 9) shows an EC_{50} of about 600 nM and a % efficacy of about 110% in the co-transfection assay; and 4-*tert*-butyl-*N*-{1-[6-methoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]ethyl}-*N*-methylbenzenesulfonamide (Example 7) shows an EC_{50} of about 300 nM and a % efficacy of about 190% in the co-transfection assay.

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.